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Chenevert et al., Tetrahedron ASsymetry (1998) 9(24) 4325-4329

Vogel et al., J. of Carbohydrate Chemistry (1992) 11(3), 287-303

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Synthesis and Lipase-Catalyzed Resolution of 5-(Hydroxymethyl)-1,3-dioxolan-4-ones: Masked Glycerol Analogs as Potential Building Blocks for Pharmaceuticals

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(Hydroxymethyl)-1,3-dioxolan-4-ones from mandelic and lactic acids and 1,5,5-trimethyl-3-phenyloxazolidin-2-one from mandelamide were α-alkylated using benzyl chloromethyl ether. Reductive debenzylation of the products of alkylation unmasked the hydroxymethyl groups. The compounds obtained in this fashion were subsequently subjected to lipase-catalyzed resolution in organic media. Depending on the lipase and substrate employed, enantiomeric ratios up to $E = 200$ were observed. The obtained optically pure compounds can be considered as masked 2-substituted glycerol equivalents, which could be used for the preparation of tertiary (aryloxy)propanolamines, compounds having potential β-blocking activity.

Introduction

Functionalized chiral C3-synthons, in particular chiral glycerol derivatives, are of much topical interest. Such compounds are used for the synthesis of several types of pharmacologically active compounds,[1] of which the antihypertensive β-adrenergic blockers are probably the most important. Several chiral derivatives of (prochiral) glycerol have been developed.

Chiral glycerol synthons can either be prepared by stereoselective synthesis from carbohydrates such as mannitol[2] or by enzymatic resolution procedures.[3] Chiral derivatives of glycerol such as the cyclic carbonate or the acetonide (solketal) have been resolved by enzymatic hydrolysis or acylation procedures.[3] Although these materials can be obtained in optically pure form this way, the chiral recognition (expressed as the enantiomeric ratio E)[4] is only moderate ($E = 5-15$), resulting in low product recovery.

The value of these materials is, however, beyond doubt. It has been shown, for example, that chiral intermediates like solketal are easily converted to the highly valuable β-blockers,[5] such as (aryloxy)propanolamines like (*S*)-propranolol.[6] The antihypertensive effect of these materials stems from their resemblance to the adrenergenic hormone (*R*)-noradrenaline, which enables them to block adrenergenic receptors.[7] The stereochemistry of these drugs is of utmost importance, and usually the (*S*) enantiomer is by far the most active.[8] The common feature of these active (aryloxy)propanolamines is that, in addition to the aryloxy and amine functionalities, they contain a secondary hydroxyl group at the chiral center. A large variety of aryloxy and amine groups has been used in the development of new β-blockers.[7] The only position at which no substituent has been introduced is at the chiral center itself where always a secondary hydroxyl group is present.

Previously, we have shown that compounds having a tertiary chiral center can be resolved efficiently by the action of enzymes. For example, we have shown that α-alkylated α-hydroxy esters are resolved by pig liver esterase (PLE) in aqueous media,[8] and that α,α-disubstituted glycols are enantioselectively acylated (at the primary hydroxyl group) by lipases in organic media.[9] We now report the synthesis and enzymatic resolution of chiral masked glycerol derivatives having an additional alkyl substituent at the chiral center. These tertiary compounds might give rise to the synthesis of a new class of (aryloxy)propanolamines having potential β-blocking properties.

Results and Discussion

A common building block used by us previously for the synthesis of both α-alkylated α-hydroxy acids and α,α-disubstituted-1,2-diols is dioxolanone **1a**. This compound is easily available from mandelic acid by transacetalization with dimethoxypropane,[9] and can be α-alkylated by deprotonation with LDA followed by trapping of the formed enolate with an electrophile. In principle, the use of formaldehyde as electrophile should lead to (hydroxymethyl)dioxolanone **2a**, which can be considered as a chiral equivalent of 2-phenylglycerol (Scheme 1) in which two of the three hydroxyl groups are masked.

The unmasked primary hydroxyl group in **2a** gives in turn a nice handle with which to perform enantioselective lipase catalyzed acylation.

As far as we are aware, compounds **2** have been described in the literature only once. They were prepared

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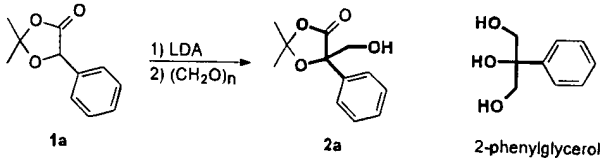
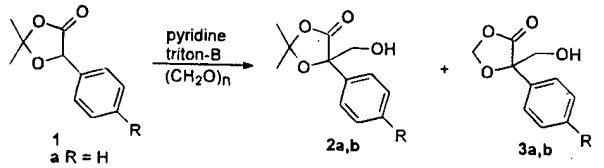
Scheme 1



1a 2a 2-phenylglycerol

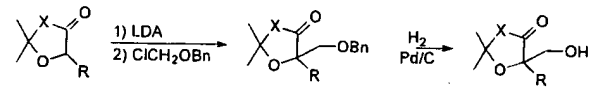
Scheme 2



1
a R = H
b R = Br

2a,b 3a,b

Scheme 3



1a (X=O; R=Ph)
4 (X=O; R=Me)
5 (X=NMe; R=Ph)

6 (X=O; R=Ph)
7 (X=O; R=Me)
8 (X=NMe; R=Ph)

	X	R	overall yield (%)
2a	O	Ph	91
9	O	Me	98
10	NMe	Ph	76

by condensation of dioxolanones **1** and paraformaldehyde in the presence of pyridine and triton-B.[10] Exact repetition of this patent procedure, however, gave only marginal yields (30%) together with a great deal of transacetalized products **3a,b** (Scheme 2).

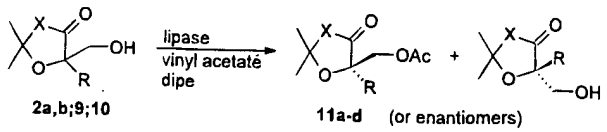
Better results were obtained by generation of the enolate of **1a**, followed by trapping with paraformaldehyde as shown in Scheme 1. Compound **2a** was obtained in higher (44%) yield, but still **3a** was produced as a major side product. An alternative (masked) hydroxymethylating reagent is benzyl chloromethyl ether.[11] Previously, it has been shown to be a powerful masked hydroxymethylating agent.[12] Alkylation of the enolate of **1a** proceeded smoothly using benzyl chloromethyl ether and gave **6** in good yield. This compound can either be purified or directly converted to **2a** by reductive hydrogenation (Scheme 3).

Via this approach, analogs **9** and **10** have been prepared as well. Owing to the fact that it is crystalline, **2b** could be obtained pure by direct condensation of dioxolanone **1b** and paraformaldehyde as shown in Scheme 2.

Resolutions of compounds **2**, **9**, and **10** were carried out by lipase-catalyzed acylation in isopropyl ether (ipe) as solvent using the enol ester vinyl acetate as acyl donor (Scheme 4).

A total of six lipases (lipases AKG and PS from Amano, pig pancreatic lipase (PPL), hog pancreatic lipase (HPL), and Candida cylindracae lipase (CCL) from Sigma and Candida antarctica lipase (CAL) from Novo) were screened for reactivity and enantioselectivity. Results are listed in Table 1.

Scheme 4



2a,b;9;10 11a-d (or enantiomers)

a (X=O; R=Ph)
b (X=O; R=4-BrPh)
c (X=O; R=Me)
d (X=NMe; R=Ph)

Table 1. Lipase-Catalyzed Resolutions of (Hydroxymethyl)dioxolanones 2, 9, and 10[a]

entry	substrate	lipase	time (h)	conv[b] (%)	ee (%) alcohol[c]	ee (%) acetate	E
1	**2a**	CCL	48	50	66 (*R*)	66	6
2	**2a**	CAL	96	32	46 (*S*)	>99	>200
3	**2a**	CAL	240	44	79 (*S*)	>99	>200
4	**2b**	CCL	20	50	80 (*R*)	60	10
5	**2b**	CAL	20	38	59 (*S*)	98	>100
6	**9**	CAL	20	60	>98 (*S*)	64	21
7	**9**	CCL	20	76	>98 (*R*)	31	7
8	**9**	HPL	68	31	38 (*S*)	86	17
9	**9**	HPL	184	47	72 (*S*)	82	20
10	**9**	PPL	20	29	38 (*S*)	91	40
11	**9**	PPL	68	46	76 (*S*)	89	40
12	**10**	CAL	72	54	>98 (*S*)	82	>50
13	**10**	CCL	184	80	59 (*S*)	15	<2

[a] Solvent isopropyl ether, temperature 20 °C. [b] Calculated from c = ee (alcohol)/(ee (alcohol)+ee (acetate). [c] See text for a discussion of the establishment of the absolute configurations.

For substrate **2a** lipases AKG, PS, PPL, and HPL gave, even after 17 days, no conversion. Of the two other lipases, CCL gave only moderate enantiodiscrimination (E = 6, entry 1), but CAL was very enantioselective giving, even at conversion approaching 50%, optically pure product **11a** (Table 1, entries 2 and 3). This corresponds to an E value of greater than 200.[13] The chiral discrimination in this kinetic resolution must therefore be nearly absolute, since it is the *product* which is obtained enantiomerically pure. It is also necessary to stress that CCL shows an opposite chiral preference for this substrate compared to CAL. Results analogous to those for **2a** were observed for bromo derivative **2b**. Again, CCL showed only moderate enantiodiscrimination (E = 10, Table 1, entry 4) and its preference was opposite to that of CAL. Enantiodiscrimination by CAL was nearly absolute, and product **11b** was obtained in 98% ee (E = 100, Table 1, entry 5). For lactic acid derivative **9**, not only CAL and CCL catalyzed transacylation, but HPL and PPL as well. This is probably due to less steric repulsion for this substrate, making it more accessible for reaction. As observed more often, the substitution of an aromatic ring by a methyl group increases reactivity, but, unfortunately, decreases chiral discrimination significantly.[9] For example, in 20 h CAL converted **9** to **11c** in 60% yield. In this way the remaining alcohol **9** is obtained enantiomerically pure (Table 1, entry 6), but at the cost of an E ratio of only 21 compared to E > 200 for **2a**.

Also, CCL was more reactive with **9**, and as for **2a,b**, the other enantiomer was converted preferentially. Enantiomerically pure **9** was obtained after 76% conversion (E = 7) using this specific lipase (Table 1, entry 7). HPL

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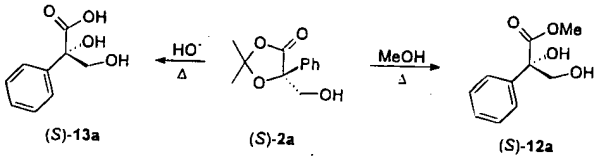
(13) In fact, for such good discriminations the logarithmic formula to calculate E can give bizarre values approaching infinity. It therefore makes no sense to give E values of greater than around 100–200 as a change in determined ee or conversions of less than 0.1% have a dramatic influence on the calculated E value.

Scheme 5



and PPL were less reactive (Table 1, entries 8–11), but especially PPL was more enantioselective. After 68 h, a conversion of 46% was achieved combined with an E of 40 (Table 1, entry 11).

A compound which is especially interesting to resolve is (hydroxymethyl)oxazolidinone **10**. Oxazolidinones like **10** already have a built-in nitrogen functionality, making them easier, via reduction, to convert to tertiary (aryloxy)propanolamines. Analogously to dioxolanones **2a,b**, **10** was resolved smoothly by CAL. At 54% conversion (72 h) the remaining alcohol had an ee of >98%, which corresponds to E > 50 (Table 1, entry 12).[14] Resolution by CCL for this specific substrate gave only the barest selectivity since E was < 2 (Table 1, entry 13)!

The absolute stereochemistry of compound **2a** was subsequently established by methanolysis to the known methyl ester **12a** (Scheme 5).

This compound had previously been prepared in optically enriched form by asymmetric dihydroxylation. It was shown by Sharpless *et al.*[15] that the enantiomeric excess of **12a** can easily be enriched by a single recrystallization. By correlation of the optical rotation of **12a** with literature values[16] the stereochemistry of **2a** resolved by CAL was established as (*S*). As lipases usually show the same enantiopreference throughout a series of analogous substrates,[16] we expect that also **2b**, **9**, and **10** have the same absolute stereochemistry as **2a**. The stereochemistry of the acetates produced by CAL must therefore be *R*.

Compound (*S*)-**2a** can also be hydrolyzed to phenylglycolic acid (*S*)-**13a** (Scheme 5). This has previously been shown to be the acid moiety in the tropane alkaloid anisodine,[17] an alkaloid showing ganglio blocking properties and used clinically for the treatment of motion sickness, migraine, and vascular spasms of fundus oculi.[18] By modification of synthetic procedures, optically active **2a** might also be used for the preparation of analogs of the antifungal agent Sch 42427.[18] We are currently exploring the possibilities of employing compounds **2**, **9**, and **10** in the syntheses of potentially active pharmaceutical compounds. Such transformations have been achieved and will be described in due course.

Conclusions and Outlook

We have shown that 5-(hydroxymethyl)1,3-dioxolan-4-ones **2** and **9** and 3-(hydroxymethyl)oxazolidine-2-one **10** are easily prepared from mandelic or lactic acid *via* their acetonides. Alkylation of the acetonide proceeds smoothly and selectively with benzyl chloromethyl ether. By reductive debenzylation compounds **2**, **9**, and **10** are obtained in overall good yields. Compounds **2a,b** and **10**, all of which have a phenyl substituent at the chiral center, are efficiently resolved by Candida antarctica lipase with E factors of up to 200. For these substrates Candida cylindracae lipase is only marginally enantioselective. Probably due to steric repulsion, four other lipases were shown not to catalyze the acylation of these compounds. The less sterically crowded **9** was also transformed by these other lipases but the enantiomeric ratios observed were somewhat lower. For this substrate the best results were obtained using pig pancreatic lipase (E = 40). By conversion of **2a** to the known methyl ester **12a** the stereochemical preference of the lipases toward substrates **2** has been established. Since both PPL and CAL are cheap and readily available lipases, this opens the way to perform resolutions on larger scale. Optimalization and scale up of the synthesis of (aryloxy)propanolamines and other potential drugs are currently in progress.

Experimental Section

All solvents were reagent grade and were dried and distilled prior to use, following standard procedures. All reagents were purchased from either Acros Chimica (previously Janssen Chimica), Aldrich, Merck, or Fluka and used without purification. Benzyl chloromethyl ether (90%) was obtained from TCI. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 or 300 MHz. ^{13}C NMR spectra (APT) were recorded at either 50.32 or 75.48 MHz. Analytical HPLC analysis was carried out using photodiode array detection. Mass spectra were recorded by EI by Mr. A. Kiewiet in our department. Elemental analyses were performed in the microanalytical group of this department by Mr. H. Draaijer, Mr. J. Ebels, and Mr. J. Hommes. Dioxolanones **1a** and **4** were prepared as described previously.[9]

5-(4-Bromophenyl)-2,2-dimethyl-1,3-dioxolan-4-one (1b). A mixture of 4-bromomandelic acid[19] (20.0 g, 86.6 mmol) and acetone (25 g) in 100 mL of benzene containing a catalytic amount of H_2SO_4 was azeotropically refluxed for 8 h. After cooling, the mixture was washed three times with a saturated $NaHCO_3$ solution followed by brine. After drying (Na_2SO_4) the solution was evaporated to dryness to yield **1b** (13.2 g, 48.9 mmol, 57% yield) mp 62.0–63.0 °C (lit.[20] 65–66 °C): ^{1}H-NMR ($CDCl_3$) δ 1.66 (s, 3H), 1.71 (s, 3H), 5.34 (s, 1H), 7.33–7.37 (m, 2H), 7.50–7.56 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 26.07 (q), 27.19 (q), 75.09 (d), 111.13 (s), 122.82 (s), 127.93 (d), 131.82 (d), 133.52 (s), 172.06 (s).

1,5,5-Trimethyl-3-phenyloxazolidin-2-one (5). Under a nitrogen atmosphere using dried glassware, 5,5-dimethyl-3-phenyloxazolidine-2-one[21] (1.91 g, 10 mmol) was dissolved in 20 mL of dry THF. After the mixture was cooled to −20 °C, KOtBu (1.12 g, 10 mmol) was added. The mixture was stirred for 5 min and methyl iodide (2.13 g, 0.93 mL, 15 mmol) was added. The mixture was stirred for 3 h and quenched with NH_4Cl solution. The reaction mixture was extracted three times with EtOAc, and the combined organic layers were washed with brine. After drying (Na_2SO_4) and evaporation a yellow oil (1.97 g, 9.6 mmol, 96% yield) was obtained which was purified by column chromatography (silica, CH_2Cl_2) to provide pure **5** (1.50 g, 7.3 mmol, 73% yield): ^{1}H-NMR ($CDCl_3$) δ 1.49 (s, 3H), 1.57 (s, 3H), 2.84 (s, 3H), 5.26 (s, 1H), 7.24–7.48 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 25.2 (q), 25.5 (q), 26.9 (q), 78.1 (d), 93.9 (s), 126.5 (d), 128.3 (d), 128.5 (d), 137.0 (s), 169.4 (s).

2,2-Dimethyl-5-(hydroxymethyl)-5-phenyl-1,3-dioxolan-4-one (2a) Using Paraformaldehyde. In a nitrogen atmosphere using dried glassware, diisopropylamine (3.5 mL, 25

(14) The ee determination of **11d** was difficult due to the peak shape of the second eluting minor enantiomer on HPLC. The ee was, therefore, conservatively estimated which results in an E of "only" 50.

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(16) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656.
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(21) Fischer, H. O. L.; Dangschat, G.; Stettiner, H. *Ber.* **1932**, *65*, 1032.

mmol) was dissolved in 50 mL of dry THF. After the mixture was cooled to −80 °C, *n*-BuLi (14 mL, 1.6 N in hexane, 22 mmol) was added. After being stirred for 15 min the mixture was recooled to −80 °C, and a solution of dioxolanone **1a** (3.84 g, 20 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min and again recooled to −80 °C. Paraformaldehyde (750 mg, 25 mmol) was added, and the mixture was slowly allowed to reach room temperature and allowed to stir overnight. Saturated NH_4Cl solution (50 mL) was added, and the reaction mixture was extracted twice with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to give crude **2a** (3.22 g, 14.5 mmol, 73% yield). This material was distilled (125 °C/0.02 mmHg) to give **2a** as a nearly pure yellow oil (1.97g, 8.87 mmol, 44% yield). For physical data see below.

2,2-Dimethyl-5-(hydroxymethyl)-5-phenyl-1,3-dioxolan-4-one (2a) via the Benzyl Ether 6. In a nitrogen atmosphere using dried glassware, diisopropylamine (10.5 mL, 75 mmol) was dissolved in 100 mL of dry THF. After the mixture was cooled to −80 °C n-BuLi (27 mL, 2.5 N in hexane, 67 mmol) was added. After being stirred for 15 min, the mixture was recooled to −80 °C and a solution of dioxolanone **1a** (11.5 g, 60 mmol) in dry THF was added dropwise. The mixture was stirred for 15 min and again recooled to −80 °C. Benzyl chloromethyl ether (90%) (10.4 mL, 65 mmol) in dry THF was added dropwise, and the mixture was allowed to reach room temperature (3 h) and stirred overnight. Saturated NH_4Cl solution (100 mL) was added, and the reaction mixture was extracted three times with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), and evaporated to give crude **6** (19.9 g) containing a small amount of benzyl alcohol. A part of this crude material (13.23 g, 42 mmol) was dissolved in 50 mL of EtOH, and 200 mg of 5% Pd on carbon was added. The mixture was hydrogenated at 40 psi for 48 h in a Parr apparatus, after which time it was filtered and evaporated to give crude **2a** (8.55 g, 38.5 mmol, 91% yield) as an oil. Pure material was obtained by bulb-to-bulb distillation (145 °C/ 0.25 mmHg), giving the title compound **2a** as a colorless oil (7.35 g, 33 mmol, 78% yield). An analytically pure sample was obtained by column chromatography (silica, ether/hexane 1:2): ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.76 (s, 3H), 2.47 (dd, J = 4.4 and 8.3 Hz, 1H), 3.67 (dd, J_{AB} = 11 HZ, J_{OH} = 4.4 Hz, 1H), 4.01 (dd, J_{AB} = 11 HZ, J_{OH} = 8.3 Hz, 1H), 7.25−7.36 (m, 3H), 7.62−7.66 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 27.56 (q), 27.91 (q), 68.13 (t), 85.23 (s), 110.91 (s), 125.06 (d), 128.56 (d), 136.11 (s). HRMS *m/z* (− CH_2O) calcd 192.079, found 192.079. Anal. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.47; H, 6.32.

The rest of crude **6** was purified by column chromatography (silica ether/hexane 1:25) to provide pure **6**: ^{1}H-NMR ($CDCl_3$) δ 1.53 (s, 3H), 1.78 (s, 3H), 3.62 (d, J_{AB} = 11 Hz, 1H), 3.92 (d, J_{AB} = 11 Hz, 1H), 4.67 (s, 2H), 7.27−7.45 (m, 8H), 7.69−7.75 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 27.44 (q), 28.18 (q), 73.65 (t), 75.14 (t), 84.10 (s), 110.58 (s), 125.20 (d), 127.50 (d), 127.66 (d), 128.36 (d), 128.45 (d), 128.52 (d), 136.18 (s), 137.50 (s); HRMS m/z calcd 312.136, found 312.136.

2,2-Dimethyl-5-(hydroxymethyl)-5-(4-bromophenyl)-1,3-dioxolan-4-one (2b).[11] Dioxolanone **1b** (5.42 g, 20 mmol) was dissolved in 35 mL of pyridine, and paraformaldehyde (2.4 g, 80 mmol) and triton-B (2 mL, 40% in MeOH) were added. The mixture was stirred overnight and cooled to −5 °C. Acetic acid was added until the pH reached 6.5−7.0, and the mixture was poured into ice−water. The slurry was extracted three times with CH_2Cl_2, and the combined organic layers were dried (Na_2SO_4). The organic fraction was evaporated on a rotary evaporator, and subsequently most of the pyridine was evaporated at low pressure (0.01 mm) at 50 °C. The remaining oil was dissolved in ether and stored overnight at 4 °C to give **2b** as white needles (1.33 g, 4.42 mmol, 22% yield): mp 131−132 °C (lit.,[11] mp 123−127 °C): ^{1}H-NMR ($CDCl_3$) δ 1.47 (s, 3H), 1.75 (s, 3H), 2.05 (br, 1H), 3.65 (d, J_{AB} = 12 Hz, 1H), 3.97 (d, J_{AB} = 12 Hz, 1H), 7.54 (s, 4H); ^{13}C-NMR ($CDCl_3$) 27.54 (q), 27.97 (q), 68.00 (t), 84.60 (s), 110.81 (s), 123.03 (s), 126.87 (d), 131.77 (d), 135.06 (s).

2,2,5-Trimethyl-5-(hydroxymethyl)-1,3-dioxolan-4-one (9). Dioxolanone **4** (2.60 g, 20 mmol) was alkylated with benzyl chloromethyl ether (3.46 mL) analogously to the procedure described above for **1a** to give **7** (5.85g, 100% yield) contaminated with benzyl alcohol. A part of the crude **7** (1.90 g, 7.6 mmol) was dissolved in EtOH and hydrogenated in a Parr apparatus with a catalytic amount of Pd/C (5%) for 48 h. After filtration, crude **9** was obtained (1.19 g, 7.44 mmol, 98% yield) of which a part was purified by column chromatography (silica, EtOAc/hexane 1:9) to give the pure title compound: ^{1}H-NMR ($CDCl_3$) δ 1.35 (s, 3H), 1.56 (s, 3H), 1.58 (s, 3H), 2.93 (br dd, J = 7.4 and 4.7 Hz, 1H), 3.50 (dd, J_{AB} = 12 Hz, J = 4.7 Hz, 1H), 3.68 (dd, J_{AB} = 12 Hz, J = 7.4 Hz, 1H); ^{13}C-NMR ($CDCl_3$) δ 20.92 (q), 27.66 (q), 28.73 (q), 66.09 (t), 81.74 (s), 110.81 (s), 174.17 (s); HRMS *m/z* (− CH_3) calcd 145.050, found 145.050.

The rest of crude **7** was purified by column chromatography (silica, EtOAc/hexane 1:9) to give a colorless oil, which solidified upon standing; mp 48−51 °C; ^{1}H-NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.53 (s, 3H), 1.57 (s, 3H), 3.45 (d, J_{AB} = 10 Hz, 1H), 3.57 (d, J_{AB} = 10 Hz, 1H), 7.26 (s, 5H); ^{13}C-NMR ($CDCl_3$) δ 21.55 (q), 27.51 (q), 28.99 (q), 73.40 (t), 80.82 (s), 110.18 (s), 127.50 (d), 127.66 (d), 128.36 (d), 137.64 (s), 173.91 (s). HRMS *m/z* calcd 250.120, found 250.120. Anal. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25. Found: C, 67.09; H, 7.23.

1,5,5-Trimethyl-3-(hydroxymethyl)-3-phenyloxazolidine-2-one (10). Using a procedure analogous to **2a** and **9**, oxazolidinone **5** (1.47 g, 7.2 mmol) was alkylated with benzyl chloromethyl ether (1.26 mL). The quantitatively obtained **8** (contaminated with benzyl alcohol) was dissolved in EtOH and hydrogenated in a Parr apparatus (72 h) using a catalytic amount of Pd/C (5%). After filtration and evaporation there remained crude **10** (1.28 g, 5.4 mmol, 76% yield). This was purified by column chromatography (silica, gradient ether/hexane 1:1 to pure ether) to provide the title compound (0.50 g, 2.13 mmol, 30% yield) as an oil which solidified upon standing: mp 87.0−89.3 °C; ^{1}H-NMR ($CDCl_3$) δ 1.39 (s, 3H), 1.82 (s, 3H), 2.60 (br, 1H), 2.83 (s, 3H), 3.60 (dd, J = 12, 4.6 Hz, 1H), 4.02 (dd, J = 12, 8.1 Hz, 1H), 7.27−7.37 (m, 3H), 7.68−7.73 (m, 2H); ^{13}C-NMR ($CDCl_3$) δ 25.62 (q), 26.61 (q), 26.90 (q), 67.89 (t), 85.92 (s), 93.70 (s), 125.55 (d), 127.89 (d), 128.15 (d), 138.70 (s). HRMS *m/z* (− CH_2O) calcd 205.110, found 205.109. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.52; H, 7.27; N, 5.98.

General Procedure for the Lipase-Catalyzed Resolution of 2. (Hydroxymethyl)dioxolanone **2** (0.3 mmol) was dissolved in a mixture of 1 mL of isopropyl ether and 0.2 mL of vinyl acetate. Lipase (20 mg) was added, and the mixture was stirred at room temperature. At regular intervals a 0.1 mL sample was taken which was filtered over celite in a Pasteur pipette. The Celite was washed with 1 mL of CH_2Cl_2, and the filtrate was evaporated to dryness. The residue was dissolved in 1 mL of isopropanol and analyzed by chiral HPLC (Daicel OJ) or GC (FS-LIPODEX C); see the supporting information for details.

Preparative Scale Resolution of (*S*)-2a Using CAL.[22] Alcohol **2a** (573 mg, 2.58 mmol) was dissolved in 10 mL of dipe and 2 mL of vinyl acetate. CAL (300 mg) was added, and the mixture was stirred at room temperature. After 19 days the lipase was removed by filtration and the filtrate was purified by column chromatography (silica ether/hexane 1:2) to yield (*S*)-**2a** (214 mg, 0.96 mmol, 73% ee) and (*R*)-**11a** (203 mg, 0.77 mmol, >99% ee) both as colorless solids.

(*S*)-2,3-Dihydroxy-2-phenylpropanoic Acid Methyl Ester (12a). Optically enriched alcohol (*S*)-**2a** (214 mg, 0.96 mmol, 73% ee) was dissolved in 10 mL of MeOH. A catalytic amount of H_2SO_4 was added, and the mixture was refluxed for 4 days. Water (10 mL) was added, and the methanol was removed by evaporation. The remaining water layer was washed three times with EtOAc, and the combined organic layers were washed with brine and dried (Na_2SO_4). After

(22) This experiment was performed only once to establish the absolute stereochemistry of **8a**. So far, no attempts have been undertaken to improve yields or shorten reaction times.

evaporation there remained (*S*)-**12a** as a colorless oil (163 mg, 0.83 mmol, 87% yield). This material was purified by column chromatography (silica ether/hexane 2:1) to yield (*S*)-**12a** as a white solid (145 mg, 0.74 mmol, 77% yield): $[\alpha]_D = -6.6°$ (*c* 1.50 in EtOH), o.p. 67% (lit.[16] $[\alpha]_D = +8.7°$ (*c* 1.05 in EtOH)) for a sample of the (*R*) enantiomer having an ee of 88%. The ee of the sample was determined as 68% by chiral HPLC (Daicel OJ-column); NMR in accordance with reference NMR.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of **2a**,**b**, **9**, and **10**, tables containing data for chiral HPLC and GC separations of compounds **2a**,**b**, **9** and **10**, **11**, and **12**, and selected HPLC chromatograms (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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Hof, Robert P. / Kellog, Richard M., J.Org.Chem., Jan 1996

Chenevert et al., Tetrahedron ASsymetry (1998) 9(24) 4325-4329

Vogel et al., J. of Carbohydrate Chemistry (1992) 11(3), 287-303

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TETRAHEDRON: *ASYMMETRY*

Regio- and enantioselectivity of the enzyme-catalyzed hydrolysis of citric acid derivatives

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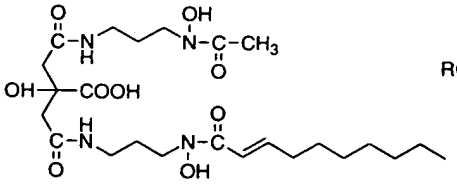
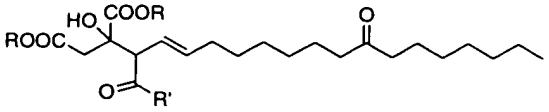
Abstract

The hydrolysis of triethyl citrate in the presence of three serine proteases (chymotrypsin, subtilisin BPN′, subtilisin carlsberg) is highly regioselective and gives the symmetric diester. Several lipases and proteases have the complementary regioselectivity and give the chiral diester. Pig liver esterase, *Aspergillus niger* lipase and *Candida antarctica* lipase give the chiral (*R*)-diester with good regio- and enantioselectivity. The stereoselective hydrolysis of the meso citric derivatives **7a,b** in the presence of *Candida antarctica* lipase gives the corresponding (*R*)-monoester.

The citric sub-unit is found in various natural products[1–8] or synthetic bioactive compounds.[9,10] For instance, rhizobactin 1021[1] (**1**) and rhizoferrin,[2,3] siderophores isolated from fungi, are chiral citrate derivatives. Viridiofungins[4] (**2**) and squalestatins[5–7] (also called zaragozic acids) are members of two families of squalene synthase inhibitors and antifungal natural products incorporating the citrate moiety. Recently, Bergeron et al.[11] reported the resolution of 1,2-dimethyl citrate by fractional crystallization of the corresponding (−)-brucine salts, and determined the absolute configuration by single crystal X-ray diffraction. Also, the citric acid derivative **8a** was resolved via fractional crystallization of the (*R*)- or (*S*)-α-methylbenzylamine salts.[12] We report here a study on the regio- and enantioselectivity of enzyme-catalyzed hydrolysis of citric acid derivatives.



1



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First, we found that the hydrolysis of triethyl citrate **3** in the presence of three serine proteases (α-chymotrypsin, subtilisin BPN′ and subtilisin carlsberg) was highly regioselective, and that the symmetric

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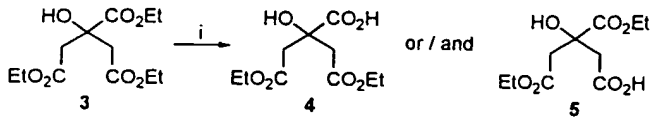
diester **4** was obtained as the sole product (Scheme 1). Anthonsen et al.[13] reported the regioselective hydrolysis of citrates by a subtilisin of unspecified origin.



Scheme 1. *Reagents*: (i) enzyme, r.t., (see Table 1)

Next, we did some screening to find enzymes which were able to distinguish the enantiotopic groups of triethyl citrate. Many lipases and proteases showed the complementary regioselectivity and gave chiral diester **5** as the sole or the major product, but the enantioselectivities were low (0–50%).[14]

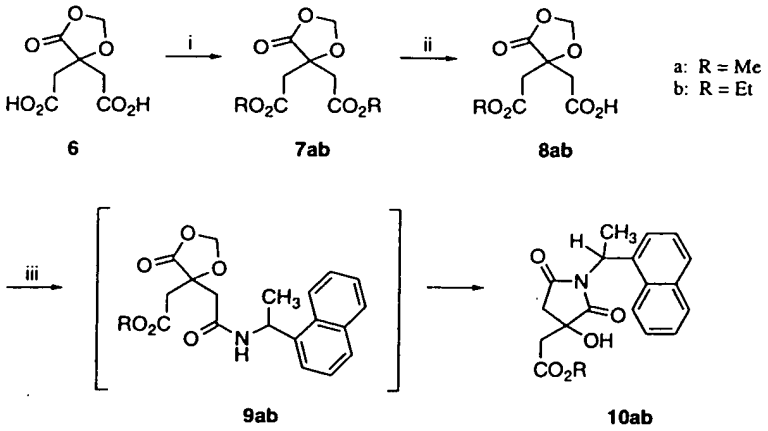
Hydrolysis of **3** in the presence of pig liver esterase (PLE) rapidly gave (2 h) the chiral diester **5** with fair regioselectivity (4/1) and good enantioselectivity (ee 90%). Lipase from *Aspergillus niger* gave **5** with high regio- (19/1) and enantioselectivity (ee 90%), but the reaction was very slow. *Candida antarctica* lipase produced **5** as the sole product with good enantioselectivity (ee 90%) in a short reaction time (3 h) (Table 1). The isomer ratio 5:4 was measured by ^{1}H NMR analysis and the diesters **4** and **5** were easily separated by standard flash chromatography. The enantiomeric composition of **5** was determined by reaction with (*S*)-(−)-(1-naphthyl)ethylamine in the presence of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC), followed by NMR analysis of the resulting diastereomeric amides.

Following from this, we investigated the desymmetrization of the citric acid derivative **7**. The diacid **6**[10] was esterified with methanol or ethanol in the presence of the corresponding 2,2-dialkoxypropane and an acidic resin to give esters **7a,b** (Scheme 2). Hydrolysis of **7a,b** in the presence of pig liver esterase in phosphate buffer provided monoesters **8a,b** in good yield (80–85%) and high enantioselectivity (ee 90–92%). The enantiomeric composition of **8a,b** was determined by reaction with (−)-(naphthyl)ethylamine in the presence of EDC, followed by NMR analysis of the resulting rearranged amides. The initially formed amides **9a,b** were rearranged to cyclic imides **10a,b** by intramolecular ring-opening of the 1,3-dioxolan-**4**-one.[15] A similar reaction was observed by Gilbert et al.[10]

The absolute configurations of **5** and **8a,b** were determined by comparison or correlation with (*R*)-(+)-**11** and (*R*)-(+)-**8a** of known absolute configurations[11,12] (Scheme 3). Ring-opening of the 1,3-dioxolan-4-one ring by refluxing **8a,b** with the appropriate alcohol and triethylamine gave (*R*)-**11** and

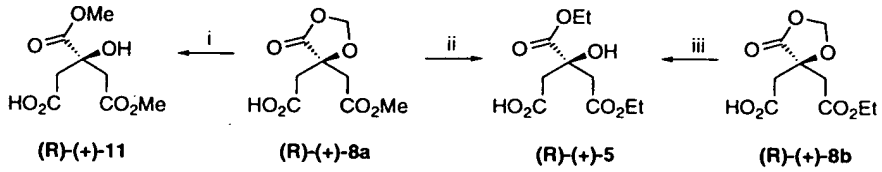
Table 1
Enzymatic hydrolysis of triethyl citrate

Enzyme	Time (days)	Yield (%)	Regioselectivity ratio 5/4	ee (%)	abs. conf.
Proteases					
Chymotrypsin	4	85	4 only	-	-
Subtilisin carlsberg	0.5	80	"	-	-
Subtilisin BPN′	4	80	"	-	-
Lipases or esterases					
Candida antarctica	3	82	5 only	90	R
Aspergillus niger	38	85	19/1	90	R
Pig liver esterase	(2 hours)	85	4/1	90	R



Scheme 2. *Reagents*: (i) ROH, H^+, $(CH_3)_2C(OR)_2$, reflux, 85%; (ii) pig liver esterase, phosphate buffer, r.t., 80%; (iii) NEA, EDC, DMAP, r.t.

(*R*)-**5**, respectively. Treatment of **8a** with sodium ethoxide in ethanol yielded **5** (ring opening and transesterification). These correlations proved that compounds **5**, **8a**,**b** have the *R* configuration.



Scheme 3. *Reagents*: (i) MeOH, Et_3N, reflux, 60%; (ii) EtONa, EtOH, r.t., 50%; (iii) EtOH, Et_3N, reflux, 60%.

1. Experimental

NMR spectra were recorded using a Bruker AC-300 instrument. Optical rotations were measured on a JASCO DIP-360 digital polarimeter (c as g of compound per 100 ml). All proteases were obtained from Sigma. Lipases were purchased from Amano International Enzyme Co. except for porcine pancreas lipase (Sigma) and *Pseudomonas fluorescens* lipase (Fluka). Pig liver esterase was from Sigma or Amano. *Candida Antarctica* lipase (novozym 435) was a gift from Novo Nordisk.

1.1. Enzymatic hydrolysis of triethyl citrate — general procedure

In a typical experiment, a suspension of triethyl citrate (150 mg, 1.84 mmol) was hydrolyzed with PLE (50 mg) in a phosphate buffer (pH 7) at room temperature. The enzymatic reaction was indicated by the decrease of pH, which was maintained at its initial value by the addition of a 0.1 M NaOH solution. The reaction was monitored by the consumption of base, and terminated when one ester equivalent was hydrolyzed. The aqueous solution was extracted with ether to remove any remaining starting material. The aqueous solution was acidified with 5 N HCl to pH 2, and the hydrolysis products were extracted with ethyl acetate. The isomeric diesters **4** and **5** were separated by flash chromatography on silica gel using hexane:ethyl acetate 4.5:5.5 as eluant. **Compound 4**: IR (neat) 3600–3040, 2980–2860, 1750, 1370, 1190, 1020, 850, 780 cm^{-1}. ^1H NMR ($CDCl_3$) 1.25 (t, J=7.1 Hz, 6H), 2.91 (m, 4H), 4.15 (q, J=7.1 Hz, 4H). ^{13}C NMR ($CDCl_3$) 177.13, 170.09, 73.16, 61.36, 42.76, 14.01. **Compound 5**: $[\alpha]_D^{25}$ +3.8 (c 1.84, MeOH); IR (neat) 3600–3040, 2980–2860, 1750, 1370, 1120, 1020, 830 cm^{-1}. ^1H NMR ($CDCl_3$)

1.25 (t, J=9.1 Hz, 6H), 2.86 (m, 4H), 4.12 (q, J=9.1 Hz, 2H), 4.28 (q, J=9.1 Hz, 2H). ^{13}C NMR ($CDCl_3$) 174.76, 174.03, 169.64, 73.12, 62.39, 60.86, 42.88, 13.89.

1.2. Preparation of 7a,b

Diacid **6**[10] (1.0 g, 4.90 mmol) was dissolved in the selected alcohol (methanol or ethanol, 20 ml), then the corresponding acetal (dimethoxypropane or diethoxypropane, 4 ml) and an acidic ion-exchange resin (Dowex 50WX4, 0.5 g) were added. The mixture was heated to reflux for 24 h. The reaction mixture was filtered to remove the resin and evaporated. The crude product was dissolved in ethyl acetate (100 ml) and washed with aq. Na_2CO_3 (2×20 ml) and brine (2×20 ml). The organic phase was dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography (AcOEt:hexane 3:10) to give corresponding diester. **Diester 7a**: yield 86%, m.p. 60–63°C; IR (KBr) 3000, 2960, 1800, 1740, 1440, 1370, 1240, 1180, 1060, 990 cm^{-1}; ^{1}H NMR (acetone-d_6) 2.97 (s, 4H), 3.66 (s, 6H), 5.50 (s, 2H); ^{13}C NMR (acetone-d_6) 174.9, 171.0, 96.3, 77.1, 52.3, 41.8. **Diester 7b**: yield 85%, oil; IR (KBr) 2980, 2930, 1800, 1740, 1375, 1180, 1060, 1020 cm^{-1}; ^{1}H NMR (acetone-d_6) 1.21 (t, J=7.0 Hz, 6H), 2.94 (s, 4H), 4.11 (q, J=7.0 Hz, 4H), 5.51 (s, 2H); ^{13}C NMR (acetone-d_6) 173.3, 169.4, 95.4, 76.3, 61.4, 41.6, 14.2.

1.3. Enzymatic hydrolysis of 7a,b

Preparation followed the general procedure described above: **7a,b** (0.43 mmol), pig liver esterase (50 mg), reaction time: 2 h. **Compound 8a**: $[\alpha]_D^{25}$ +8.4 (c 2.46, MeOH); IR (KBr) 3500–2500, 1790, 1720, 1180, 1145, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) 2.90 and 2.95 (2s, 4H), 3.71 (s, 3H), 5.55 (s, 2H), 7.97 (s, 1H); ^{13}C NMR ($CDCl_3$) 173.4, 172.8, 168.9, 95,0, 75.3, 52.2, 40.8. **Compound 8b**: $[\alpha]_D^{25}$ +10.2 (c 1.84, MeOH); IR (KBr) 3500–2500, 1790, 1720, 1180, 1145, 1000 cm^{-1}; ^{1}H NMR ($CDCl_3$) 1.20 (t, J=7.0 Hz, 3H), 2.83 and 2.89 (2s, 4H), 4.10 (q, J=7,0 Hz, 2H), 5.49 (s, 2H), 8.92 (s, 1H); ^{13}C NMR ($CDCl_3$) 173.6, 172.8, 168.4, 75.3, 61.3, 41.1, 40.8, 13.9.

1.4. Ring opening of compound 8a,b

Compound **8a** or **8b** (0.85 mmol) was dissolved in dry methanol or ethanol (20 ml). Freshly distilled triethylamine (236 µl, 1.70 mmol) was added and the solution was heated at reflux for 24 h. After allowing to cool to room temperature, the solution was evaporated to dryness. The excess of amine was neutralized with 1 N HCl. The aqueous solution was extracted with ethyl acetate (4×15 ml). The organic solution was washed with brine (2×20 ml), dried ($MgSO_4$) and evaporated to yield **5** or **11**. **Compound 5**: $[\alpha]_D^{25}$ +3.8 (c 1.84, MeOH), data described earlier. **Compound 11**: $[\alpha]_D^{25}$ +3.9 (c 1, MeOH); lit.[11,12] $[\alpha]_D^{25}$ +4.0 (c 1, MeOH). Spectral data are in agreement with those reported in the literature.[10,11]

1.5. Ring opening and transesterification of compound 8a

Sodium (47 mg, 2.06 mmol) was added to dry ethanol cooled to 0°C. A solution of **8a** (180 mg, 0.825 mmol) in dry ethanol was added and the mixture was allowed to warm to room temperature and stirred overnight. The solution was evaporated to dryness and the residue was dissolved in ethyl acetate. The organic layer was neutralized with 1 N HCl and washed with brine. The organic phase was dried ($MgSO_4$) and evaporated to give **5** ($[\alpha]_D^{25}$ +3.8 (c 1.84, MeOH)).

Acknowledgements

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14. Proteases: *Serratia* sp., *Bacillus thermoproteolyticus rokko*, *Bacillus polymyxa*, *Aspergillus saito*, *Rhizopus* sp., *Streptomyces griseus*. Lipases: *Pseudomonas cepacia*, *Mucor* sp., *Geotricum candidum*, *Rhizopus* sp., *Rhizopus niveus*, *Pseudomonas fluorescens*, *Pseudomonas* sp., *Candida* sp., *Penicillium* sp., porcine pancreas.
15. Data for compound **10a** (one diastereoisomer): IR (KBr) 3420, 1780, 1700 cm^{-1}; ^1H NMR (acetone-d_6) 1.89 (d, J=7.0 Hz, 3H), 2.57 (d, J=18 Hz, 1H), 3.10 (m, 3H), 3.49 (s, 3H), 6.10 (q, J=7.0 Hz, 1H), 7.48 (m, 3H), 7.88 (m, 3H), 8.10 (m, 1H). ^{13}C NMR (acetone-d_6) 178.7, 175.0, 170.9, 135.5, 134.6, 132.1, 129.5, 129.0, 127.1, 126.8, 126.2, 125.8, 123.8, 72.5, 51.9, 47.1, 42.4, 41.2, 17.2.

STIC-ILL 464,904 vol no 9/23

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Synthesis and lipase-catalyzed resolution of 5-(hydroxymethyl)-1,3-dioxolan-4-ones: masked analogs as potential building...
Hof, Robert P. / Kellog, Richard M., J.Org.Chem., Jan 1996

Chenevert et al., Tetrahedron ASsymetry (1998) 9(24) 4325-4329

Vogel et al., J. of Carbohydrate Chemistry (1992) 11(3), 287-303

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CAS 9/23

J. CARBOHYDRATE CHEMISTRY, 11(3), 287-303 (1992)

SYNTHESIS, CRYSTAL STRUCTURE, AND SOME REACTIONS OF 2,3,4-TRI-O-ACETYL-ß-D-GALACTOPYRANURONO-6,1-LACTONE

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Received April 16, 1991 - Final form December 4, 1991

ABSTRACT

D-*Gluco*-, D-*galacto*-, and D-*manno*-configurated 6,1-lactones of uronic acid were synthesized. A new synthetic approach based on the photobromination, hydrolysis, and oxidation of the corresponding 1,6-anhydro sugars is reported. Conformational studies of 2,3,4-tri-*O*-acetyl-ß-D-galactopyranurono-6,1-lactone in crystalline form and in solution were undertaken. First results of selective deacetylation catalyzed by wheat germ lipase are reported.

INTRODUCTION

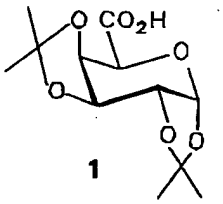
In order to understand the physiological role of dietary fibre in man[2] and the defense mechanisms of plants which can be induced by cell-wall material,[3] oligosaccharides, especially pectin fragments, should be available for biological studies. The isolation procedure of such fragments of defined structure from natural sources is often cumbersome and thus, several research groups are investigating effective approaches for the synthesis of oligosaccharides composed mainly of D-galacturonic acid.

Two fundamental routes of synthesis of D-galacturonic acid oligomers are known. The method of T. Ogawa et al.[4-7] is based on the formation of D-galactose oligomers with the desired *O*-glycosidic bonds while the hydroxymethyl group is

temporarily protected. In a separate operation oxidation of hydroxymethyl to carboxyl leads to the D-galacturonic acid oligomers.

The second principal route for oligomer preparation starts with intact D-galacturonic acid precursors suitable for use in glycosidation reactions. Accepting the challenge of the second route, we began a program aimed at the synthesis of D-galacturonic acid derivatives which can be used either as glycosyl donors or as glycosyl acceptors.

SCHEME 1



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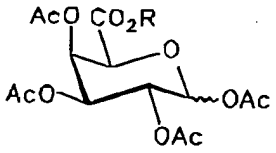
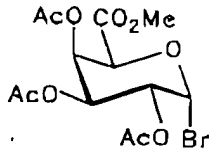


2 : R= Me
3 : R= Bn
4 : R= p-NO_2-Bn



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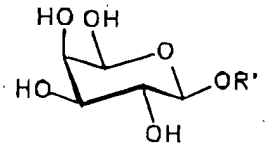
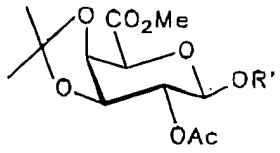


6 : R'= All
7 : R'= Bn



8 : R'= All
9 : R'= Bn

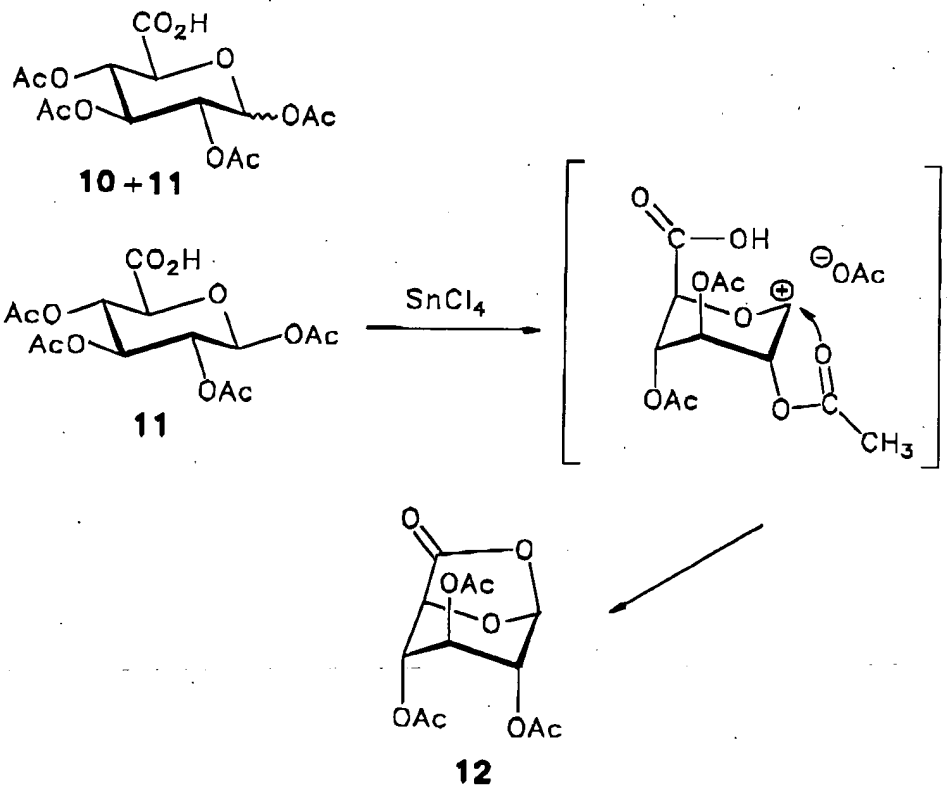
Several approaches based on D-galactose precursors have been previously reported. We reinvestigated the oxidation of 1,2;3,4-di-*O*-isopropylidene-α-D-galactopyranose to the corresponding D-galacturonic acid derivative **1**. However, only when conditions of acetolysis were used for the de-*O*-isopropylidenation step, alkyl (1,2,3,4-tetra-*O*-acetyl-α/ß-D-galactopyranose) uronates (**2-4**) could be obtained in an acceptable yield.[8] The latter compounds are simple starting-materials for glycosyl donors (e.g. **5**). By using allyl and benzyl D-galactopyranosides (**6** and **7**) as precursors we were able to prepare "standardized intermediates" (**8** and **9**) for glycoside synthesis with galacturonic acid derivatives.[9]

The present article describes the synthesis of acetylated D-galacturonic acid 6,1-lactone using the corresponding 1,6-anhydro-ß-D-galactopyranose as a precursor and the possibility of extending this reaction to *gluco-* and *manno-* configurated 1,6-anhydropyranoses.

RESULTS AND DISCUSSION

Repeating units in pectin fragments are often α-(1 → 4) linked. For activation of the axial hydroxyl group in the 4-position the natural $^4C_1$ conformation of *galacto*-configurated glycosyl acceptors is converted into the $^1C_4$ conformation fixed as a 1,6-anhydro-structure leading to a more reactive equatorial hydroxyl group in the 4-position.[10] Therefore, we turned our attention to uronic acid 6,1-lactones, where previously only the acetylated D-glucopyranurono-6,1-lactone **12** was described. The approach by E. M. Fry was based on the conversion of tetra-*O*-acetyl-ß-D-glucuronic acid **11** in the presence of stannic chloride into the corresponding 6,1-lactone.[11]

SCHEME 2

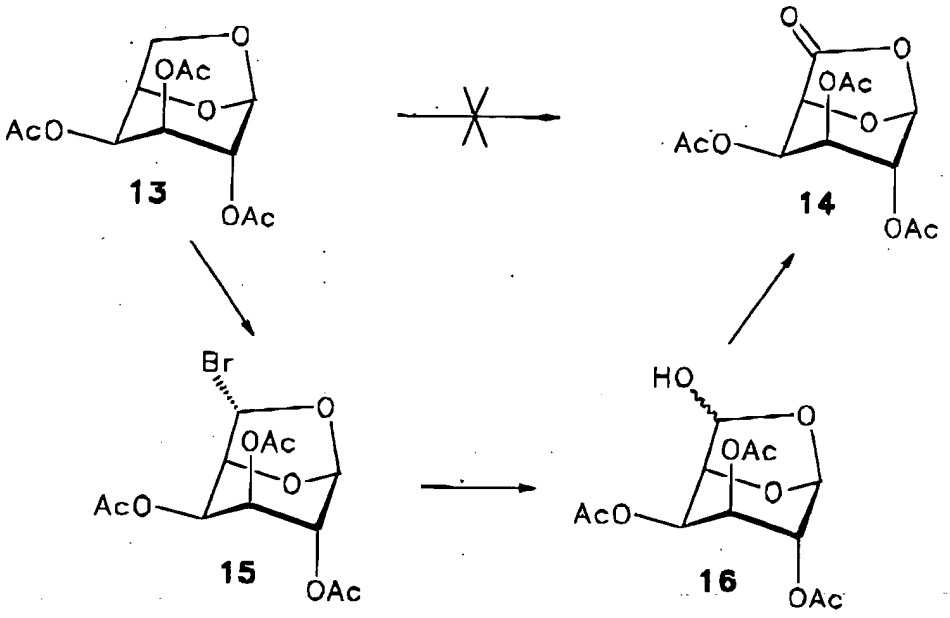


Our initial experiments focused on the ruthenium (VIII) oxide oxidation of the readily available 2,3,4-tri-*O*-acetyl-1,6-anhydro-ß-D-galactopyranose **13**[12] to the lactone **14**. This reagent has been applied successfully to oxidation of methylene

groups adjacent to ether oxygens in other fused ring systems.[13-15] Unfortunately, in our case no reaction occurred, although several modified reaction conditions were tested.

The key step in an alternative route to **14** was the introduction of bromine into the 6-position of compound **13** by the Ferrier-Ohrui reaction[16-19] which led to the derivative **15**. Consequently, the carbon-6-atom of compound **15** was anticipated to have comparable properties to a bromine-substituted carbon atom at the anomeric centre. As expected, in ^{13}C NMR spectra the carbon-6-signal at δ 64.3 ppm from **13** was shifted downfield at δ 82.6 ppm for compound **15**. These data are consistent with our experimental results wherein **15** was readily hydrolyzed to **16** on treatment with moist silver salts.

SCHEME 3

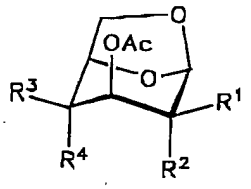


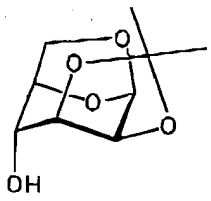
Subsequent oxidation of hemiacetal **16** with pyridinium dichromate (PDC) gave the desired 6,1-lactone **14** in 71% yield based on 1,6-anhydro derivative **13**. The same procedure was applied to the synthesis of glycuronic acid 6,1-lactones **12** and **22** derived from corresponding acetylated 1,6-anhydropyranoses of D-glucose (**17**) and D-mannose (**18**) in 59% and 52% yield, respectively. In order to obtain pure acetylated 1,6-anhydro-ß-D-mannopyranose **18** the crude product was deacetylated,

and then treated with acetone to afford 1,6-anhydro-2,3-*O*-isopropylidene-ß-D-mannopyranose **19**, purified by crystallization. De-*O*-isopropylidenation followed by acetylation led to the clean starting material for the preparation of **22**.[20]

This method of synthesis of 6,1-lactones compares favorably to the earlier reported synthesis of **12**[11] which has several troublesome steps, especially the separation by fractional crystallization of the ß-anomer of tetra-*O*-acetyl-glucuronic acid from the α-anomer which gave only moderate yields of the desired product.

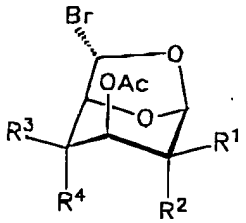
SCHEME 4

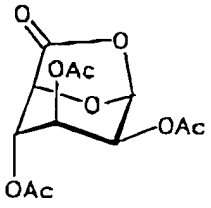


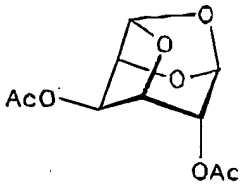


17 : R^1, R^3= H; R^2, R^4= OAc
18 : R^2, R^3= H; R^1, R^4= OAc

19







20 : R^1, R^3= H; R^2, R^4= OAc
21 : R^2, R^3= H; R^1, R^4= OAc

22

23

The IR spectra, the ^1H NMR data and ^{13}C NMR data for the 6,1-lactone **14** are in full accord with the proposed structure. The IR spectrum contained a new peak at 1835 cm^{-1} assignable to C=O band and the C-O stretching vibrations of a γ-lactone indicating that this compound is a 6,1-lactone.

A comparison with the ^1H NMR spectra of the 1,6-anhydro sugar **13** shows that for **14** both signals of H-6_{exo} and H-6_{endo} disappeared. Coupling between pyranosyl proton resonances were assigned by using homonuclear correlated spectroscopy (COSY, 500 MHz) and all sets of resonances were determined by tracing out the

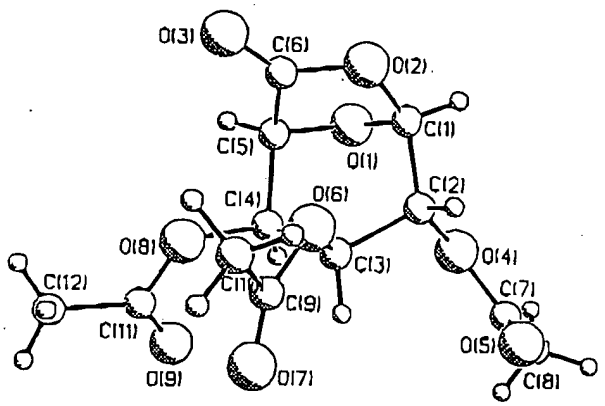


Fig. 1. Parallel projection of **14** oriented optimally.

coupling network. The anomeric proton is at the lowest magnetic field at δ 5.86 ppm exhibiting a strong correlation with the signal at δ 4.98 ppm (H-2) and a weak correlation with the signal at δ 5.43 ppm (H-3). The signal at δ 4.34 ppm (H-5) is linked with the signals at δ 5.36 ppm (strong; H-4) and at δ 5.43 ppm (weak; H-3). Further, a connection exists between signals at δ 5.43 ppm (H-3), at δ 4.98 ppm (H-2) and at δ 5.36 ppm (H-4).

X-ray studies were undertaken to establish the structure of **14** and to obtain information on the conformation of the pyranose ring. The crystals of **14** are trigonal, uncommon for a simple organic molecule. A good view (Fig. 1) is difficult to find, from every view point some atom lies in front of another. According to the X-ray studies, the $^1C_4$ conformation is present in the crystal state for **14**. From the literature is known that the 1,6-anhydro sugars have rigid skeletons in solution,[21,22] illustrated by nearly temperature independence of ^{1}H-chemical shifts, coupling constants, and spectral line width of the spectra for **13** and **14**. In no case was a chair-boat transition ($^1C_4 \rightarrow B_{0,3}$) observed.

Nevertheless, conformational differences exist between crystal state and solution as suggested by poor agreement of calculated vicinal coupling constants for the pyranosyl protons of **14** (particularly, $J_{2,3}$ and $J_{4,5}$) obtained by application of Karplus type equations and observed coupling constants from the ^{1}H NMR spectra. Thus, a more distored $^1C_4$ chair conformation of the pyranose ring in solution is indicated. The values of $^3J_{H,H}$ were obtained from the following equation:

$$^3J = 5.95 - 1.35 \cos \phi + 5.45 \cos 2\phi - 0.45 \cos 3\phi.$$[21]

TABLE 1

Conformational Parameters for Hydrogen Atoms of Compound **14**

	X-ray data			^{1}H NMR data	
	detected dihedral angle	calculated vic.-coupling constants		detected vic.-coupling constants	calculated dihedral angle
		Karplus	Altona		Karplus
H-1 / H-2	-66.4°	1.3 Hz	1.1 Hz	1.4 Hz	-65°
H-2 / H-3	85.8°	0.4 Hz	0.4 Hz	1.6 Hz	117°
H-3 / H-4	40.4°	4.3 Hz	5.0 Hz	4.6 Hz	43°
H-4 / H-5	-71.0°	1.2 Hz	0.3 Hz	4.3 Hz	-45°

This equation was corrected for the electronegativities, according to the relationship $^3J_{cor} = {}^3J \times (1 - 0.1 \Sigma \Delta E_i)$ utilizing Pauling's values for electronegativities $E_H = 2.1$, $E_C = 2.5$ and $E_O = 3.5$. A second set of calculated $^3J_{H,H}$ values was obtained by using the equation proposed by Altona.[23] Calculated vicinal-coupling constants $^3J_{H,H}$ (Hz) from values for dihedral angle $\phi_{H,H}$ from crystal-structure data for **14** were compared with the observed vicinal coupling constants from ^{1}H NMR spectra. Additionally, the appropriate dihedral angle $\phi_{H,H}$ was determined from the ^{1}H NMR data by application of the Karplus type equations,[24] $^3J_{H,H} = 9.26 \cos^2 \phi - 28$ (Table 1).

It seems noteworthy that the values $J_{4,5}$ in **D-*galacto***, **D-*gulo***, **D-*talo*** and **D-*ido*** configurated 1,6-anhydro sugars show nearly equal magnitudes (4.2 ± 0.3 Hz) attributed to the effects of oxygen substituent in equatorial orientation, revealing a chair deformation to a E_0 envelope form.[21] The same trend is apparent in the determined $J_{2,3} = 1.6$ Hz and the corresponding calculated dihedral angle $\phi_{2,3} \approx 117°$. In contrast, a decrease in the magnitude of $\phi_{3,4}$ expected from models, was not observed.

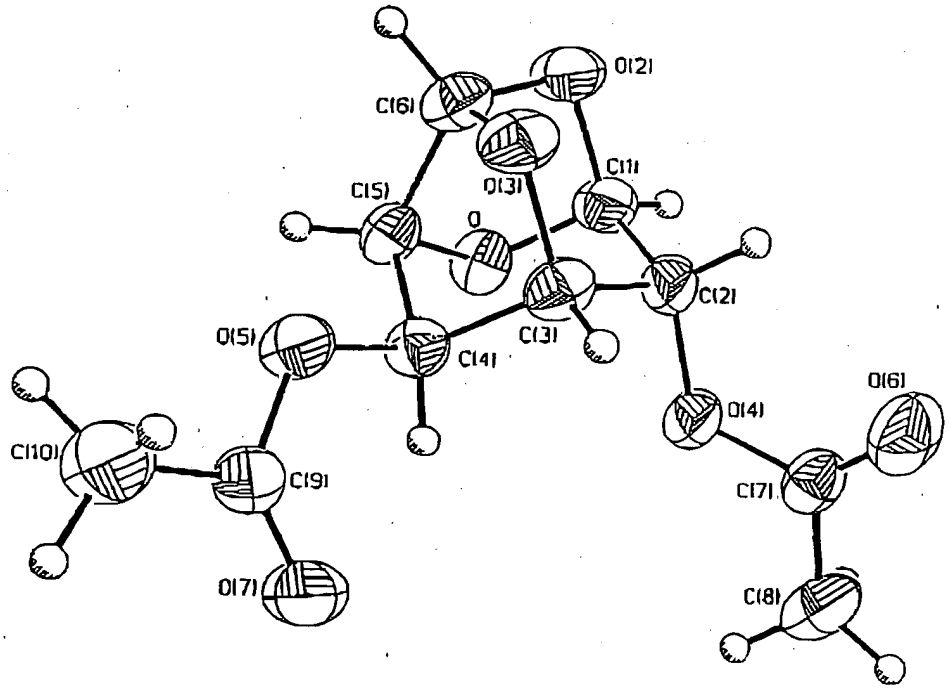


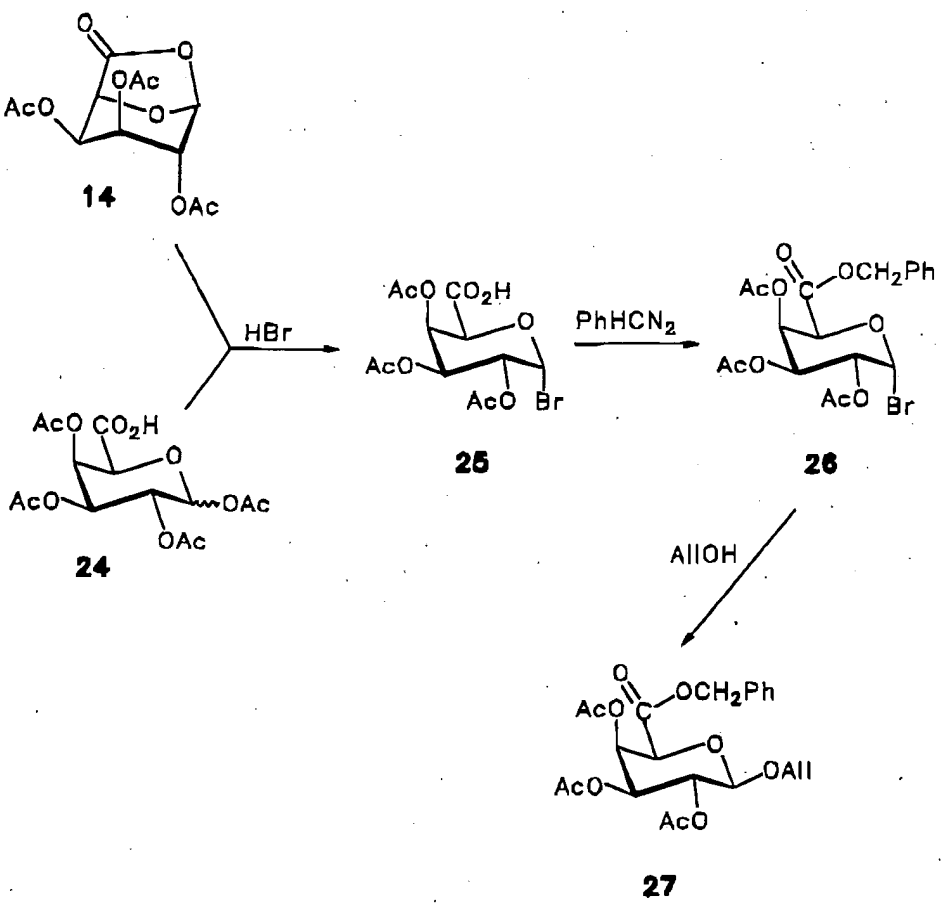
FIG. 2. An ORTEP diagram of **23**.

Consideration of the results of a computer modeling of **14** has demonstrated that the Karplus equation is to be used only with restriction in such conformationally locked ring-systems. Nevertheless, we can draw the conclusion that the pyranose ring of **14** is more flattened from the $^1C_4$ chair to the envelope form in solution than in crystal, following the common trend in 1,6-anhydro sugar series.[25] Hence, a $B_{0,3}$ boat form should be ruled out.

We also began a separate investigation to elongate the carbon skeleton of 1,6-anhydropyranoses by nucleophilic displacement of bromine in compound **15**. However, treatment of **15** with mercury(II)cyanide in nitromethane gave the crystalline tricyclic acetal **23**.

The ^1H NMR spectra of compound **23** showed only two acetyl methyl proton signals, while the ^{13}C NMR spectra showed two carbonyl carbon and two acetyl methyl carbon resonances. Additionally, a strong down-field shift of C-6 to δ 100.4 ppm compared to compound **13** suggested that C-1 and C-6 in **23** have more or less the same magnetic environments.

SCHEME 5



Finally, the structure of **23** has been verified by X-ray diffraction analysis with direct methods by use of a modified version of the NICOLET P3 program. A steric view of the molecular structure of **23** is shown in Fig. 2. The pyranose ring has the expected chair conformation $^1C_4(D)$.

The reported new method for the preparation of D-*gluco*-, D-*galacto*-,and D-*manno* configurated 6,1-lactones of uronic acid based on the photobromination, hydrolysis, and oxidation of the corresponding 1,6-anhydro sugars has significantly improved the access to this class of substances. Unfortunately, our attempts to use D-galacturonic acid 6,1-lactone as a fertile synthetic intermediate in nucleophilic reactions failed completely.

Treatment of **14** with alcohols, amines or hydrazine resulted in either a complex mixture of products or with no reaction occurring. Only the conversion into the known (tri-*O*-acetyl-α-D-galactopyranosyl bromide) uronic acid **25** by the action of hydrogen bromide in acetic acid succeeded. The reaction proceeded in full analogy to that described by Fry,[11] however, an alternative approach to **25** illustrated in Scheme 5 has been shown[26] to be much shorter.

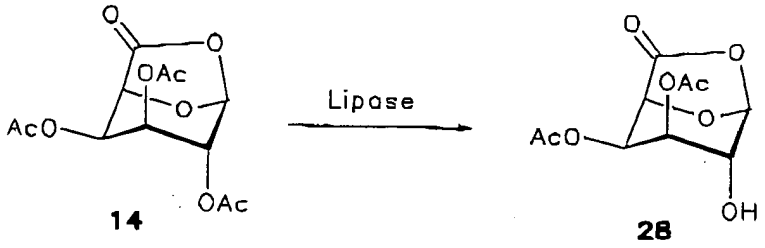
It may be noted that compound **25** offers the possibility for introduction of an acid-labile ester group into pyranosyl bromides of uronic acid (e.g. **26**). As expected, the reaction of **26** with allyl alcohol in the presence of $Hg(CN)_2$ / $HgBr_2$ afforded successfully the corresponding acetylated benzyl (allyl ß-D-galactopyranosid) uronate **27**.

In attempting to prepare a galacturonic acid glycosyl acceptor from **14** *O*-deacetylation of **14** was unavoidable. All attemps with chemical methods to achieve either a partial regioselective deacetylation or a complete deacetylation were unsuccessful and lead to an unidentified mixture of products. We propose a rapid lactone ring opening reaction under these conditions because in the IR spectra of the products the C=O band at 1835 cm^{-1} disappeared.

Only enzyme-catalyzed hydrolysis[27-29] resulted in partially esterified derivatives. When compound **14** dissolved in *N,N*-dimethylformamide was treated with wheat germ lipase purchased from SIGMA Chemical Co. in K_2HPO_4 buffer (pH 7) formation of a new product was observed after 4 hours. The *O*-2 acetyl group of **14** was removed to give 3,4-di-*O*-acetyl-ß-D-galactopyranurono-6,1-lactone **28** in 19% yield.

Inspection of the ^1H NMR spectrum supported this conclusion, as only two methyl acetyl proton signals were observed. The assignment of the proton coupling network in **28** was accomplished from a two-dimensional COSY spectrum, which provided the key information that the chemical shift of H-2 of **28** was at significantly higher field compared with the signal of the starting material **14**.

SCHEME 6



Thus, the general applicability of partial deprotected galacturono-6,1-lactones in glycosidation reactions has to be tested, and then we hope to find enzymes for selective *O*-deacetylation at C-4.

EXPERIMENTAL

General Procedures. See ref. 9. NMR spectra were recorded with a Bruker spectrometer model WH-250 at 250 MHz for ^1H, and 62.89 MHz for ^{13}C, Bruker WH 270 at 270 MHz for ^1H, and 67.89 MHz for ^{13}C, Bruker WM-400 (400 MHz), and Bruker WM-500 (500 MHz) for ^1H. X-ray diffraction measurements were performed on a Nicolet R3m/E diffractometer system, the diffraction data were collected with intensities from Θ:2Θ scans by use of a profile-fitting procedure. A graphite monochromatic MoKα radiation (wavelength = 0.71073 Å) was used. A modified version of the Nicolet P3 data collection progam was applied and the SHELXTL 5.1 system was used for data reduction, structure solution, refinement, and preparation of graphics and tables [Sheldrick, G. M. (1985). SHELXTL. Release 5.1. Nicolet Analytical Instruments, Madison, Wisconsin, U.S.A.].

The crystals of compound **14** are trigonal, space group $P3_2$, with 3 molecules in a hexagonal cell of dimensions a= 8.4902 (0.033) and c= 17.1980 (0.100) Å. The crystals of compound **23** are monoclinic, space group $P2_1$, Z= 2, a= 10.065(2), b= 5.488(1), c= 10.214(2) Å, ß= 105.21(2)°, V= 544.4(2) Å^3. Additional diffractometer parameters are as follows: linear absorption coefficient, μ= 1.20 cm^{-3}; F(000), 256; temperature of measurement, room temperature; final R-factors, R = 0.039, wR = 0.047; number of unique observed reflections, 1356; lattice parameters from 25 reflections in the range 25<2Θ< 30°, no absorption correction; maximum (sin Θ/λ in intensity measurements, 0.65 Å^{-1}); range of h, k, l were 0 - 14, 0 - 8, -14 - 14; standard reflections, 3 standards after every 97 reflections; number of reflections measured, 1518 including standards; number of unique observed reflections, 1356 with I > 1.0 σ(I); value of R_{int}= Σ | F -<F> | / Σ F, from merging equivalent reflections, 0.013. All H atoms were found on the difference map (with some uncertainty in the methyl groups). H atoms inserted in theoretical positions and refined in the model, except methyl groups which were treated as rigid groups. The isotropic thermal parameter was taken as about 20% more than for the C atom to which the H atom was bonded. Parameters refined, 160; goodness of fit, 2.13; structure-factor weights, w= 1/[σ^2(F) + 0.00020 F^2] with σ^2(F) from counting statistics; maximum ratio of least-squares shift to e.s.d in final cycle, 0.16; no extinction correction; f_0, f', f" from International Tables for X-Ray Crystallography (1974) Vol. IV. Detailed X-ray data will be supplied on request to authors.

The following solvent systems (v/v) were used for chromatography: (A_1) 3:2, (A_2) 2:1, (A_3) 2:3 and (A_4) 4:1 PhMe-EtOAc.

Photobromination of 1,6-Anhydro-2,3,4-tri-O-acetyl-D-hexopyranose. A mixture of 1,6-anhydro-2,3,4-tri-*O*-acetyl-ß-D-hexopyranose (**13**, **17** or **18**, 2.02 g, 7 mmol) and bromine (0.8 mL, 16 mmol) in dry CCl_4 (100 mL) was refluxed over a 250 W heat lamp for 3-4 h (TLC, solvent A_1). The cooled solution was successively washed with 10% aq. $Na_2S_2O_3$ (2 x 50 mL), sat. aq. $NaHCO_3$ (2 x 50 mL), water (2 x 50 mL), and dried over $MgSO_4$. Evaporation of the solvent in vacuo below 30 °C gave a syrup which was dissolved twice in dry ether (50 mL) and reconcentrated to give the corresponding 6-bromo compound.

(6S)-1,6-Anhydro-2,3,4-tri-O-acetyl-6-bromo-ß-D-galactopyranose (15). (2.18 g, 85%), syrup, $[\alpha]_D^{21}$ -61.7° (*c* 0.98, chloroform); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6 (3 C, $\underline{C}H_3CO$), 64.4, 66.9, 69.3, 79.9 (C-2, C-3, C-4, C-5), 82.6 (C-6), 101.7 (C-1),168.8, 169.2, 169.5 (3C, $CH_3\underline{C}O$).

Anal. Calcd for C_{12} H_{15} O_8 Br: C, 39.26; H, 4.12. Found: C, 39.5 ; H, 4.2 .

(6S)-1,6-Anhydro-2,3,4-tri-O-acetyl-6-bromo-ß-D-glucopyranose (20). (2.49 g, 97%), syrup, $[\alpha]_D^{21}$ -69.1° (*c* 0.85, chloroform).

Anal. Calcd for C_{12} H_{15} O_8 Br: C, 39.26; H, 4.12. Found: C, 39.6 ; H, 4.3 .

(6S)-1,6-Anhydro-2,3,4-tri-O-acetyl-6-bromo-ß-D-mannopyranose (21). (2.42 g, 94%), mp 86 °C (from light petroleum); $[\alpha]_D^{21}$ -80.8° (*c* 1.0 , chloroform).

Anal. Calcd for C_{12} H_{15} O_8 Br: C, 39.26; H, 4.12. Found: C, 39.3 ; H, 4.1 .

Tri-O-acetyl-ß-D-glycopyranurono-6,1-lactones. To a suspension of 1,6-anhydro-2,3,4-tri-*O*-acetyl-6-bromo-ß-D-hexopyranose (**15**, **20** or **21**, 1.84 g, 5 mmol) and freshly prepared Ag_2CO_3 (1.25 g, 4.5 mmol) in dry acetone (10 mL) was added water (0.1 mL, 5.5 mmol). After vigorous stirring for 2 h at ambient temperature in the dark (TLC, solvent A_1), the mixture was filtered through Celite and concentrated. The residue was successively co-evaporated with toluene (2 x 50 mL) and ethanol (2 x 50 mL) and then dried in high vacuum for 3 h. A freshly prepared solution of pyridinium dichromate (1.13 g, 3 mmol) and acetic anhydride (1.4 mL) in dry dichloromethane (10 mL) was added to a solution of the obtained syrup, which was sufficiently pure for the next step, in dry dichloromethane (10 mL). After the reaction mixture was stirred for 3 h at ambient temperature (TLC, solvent A_1) it was passed through a layer of silica gel (2 x 3 cm) with ethyl acetate, and the eluent gave a syrupy residue, which was co-evaporated several times with toluene and then crystallized from ethanol.

2,3,4-Tri-O-acetyl-ß-D-glucopyranurono-6,1-lactone (12). (0.91 g, 60.1%), mp 122-123 °C, $[\alpha]_D^{20}$ -73.6° (*c* 1.0, chloroform); lit.[11] mp 123-124 °C, $[\alpha]_D^{19}$

-78.6° (*c* 0.9, chloroform); lit.[25] mp 127 °C, $[\alpha]_D^{20}$ -66.0° (*c* 2, chloroform); IR max 1825 (C=O str. 6,1-lactone) 1755, 1770 cm^{-1} (C=O str. OAc); ^1H NMR ($CDCl_3$) δ 2.11, 2.18 (2 s, 9 H, $C\underline{H}_3CO$), 4.62 (t, 1 H, H-5), 4.79 (dd, 1 H, $J_{2,3}$= 2.4 Hz, $J_{2,4}$= 1.4 Hz, H-2), 4.83 (dd, 1 H, $J_{4,5}$= 1.6 Hz, H-4), 4.97 (m, 1 H, $J_{3,4}$= 2.6 Hz, H-3), 5.94 (t, 1 H, $J_{1,2}$ = $J_{1,3}$= 1.2 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.7 (3 C, $\underline{C}H_3CO$), 65.9 (C-2), 66.1 (C-4), 69.0 (C-3), 71.2 (C-5), 100.5 (C-1), 167.9 (C-6), 168.7, 169.4 (3 C, $CH_3\underline{C}O$).

Anal. Calcd for $C_{12}H_{14}O_9$: C, 47.69; H, 4.67. Found: C, 47.8 ; H, 4.8.

2,3,4-Tri-O-acetyl-ß-D-galactopyranurono-6,1-lactone (14). (1.27 g, 83.5%), mp 99-100 °C, $[\alpha]_D^{20}$ -11.5° (*c* 1.0, chloroform); IR max 1835 (C=O str. 6,1-lactone) 1750, 1770 cm^{-1} (C=O str. OAc); ^1H NMR ($CDCl_3$) δ 2.08, 2.12, 2.18 (3 s, 9 H, $C\underline{H}_3CO$), 4.34 (dd, 1 H, H-5), 4.97 (t, 1 H, $J_{2,3}$= 1.6 Hz, $J_{2,4}$= 1.6 Hz, H-2), 5.35 (t, 1 H, $J_{4,5}$= 1.6 Hz, H-4), 5.42 (m, 1 H, $J_{3,4}$= 4.6 Hz, $J_{3,5}$= 1.6 Hz, H-3), 5.86 (t, 1 H, $J_{1,2}$= $J_{1,3}$= 1,5 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.5, 20.7 (3 C, $\underline{C}H_3CO$), 64.7 (C-2), 67.5 (C-3), 68.5 (C-4), 68.9 (C-5), 100.2 (C-1), 169.0 (C-6), 169.3 (3 C, $CH_3\underline{C}O$).

Anal. Calcd for $C_{12}H_{14}O_9$: C, 47.69; H, 4.67. Found: C, 47.7 ; H, 4.9 .

2,3,4-Tri-O-acetyl-ß-D-mannopyranurono-6,1-lactone (22). (0.84 g, 55.3%), syrup, $[\alpha]_D^{20}$ +7.9° (*c* 0.8, chloroform); IR max 1835 (C=O str. 6,1-lactone) 1720, 1730 cm^{-1} (C=O str. OAc); ^1H NMR ($CDCl_3$) δ 2.10, 2.12, 2.19 (3 s, 9 H, $C\underline{H}_3CO$), 4.59 (t, 1 H, H-5), 4.94 (t, 1 H, $J_{4,5}$= 1.6 Hz, H-4), 5.26 (dd, 1 H, $J_{2,3}$= 5.2 Hz, H-2), 5.47 (m, 1 H, $J_{3,4}$= $J_{3,5}$= 1.6 Hz, H-3), 5.87 (t, 1 H, $J_{1,2}$= $J_{1,3}$= 1.6 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6, 20.7 (3 C, $\underline{C}H_3CO$), 64.5 (C-2), 67.3 (C-3), 67.6 (C-4), 71.3 (C-5), 101.6 (C-1), 168.1 (C-6), 169.1, 169.2, 169.4 (3 C, $CH_3\underline{C}O$).

Anal. Calcd for $C_{12}H_{14}O_9$: C, 47.69; H, 4.67. Found: C, 47.8 ; H, 5.0 .

2,4-Di-O-acetyl-1,6;3,6-dianhydro-D-galacto-hexo-di-aldopyranose (23). To a stirred solution of 2,3,4-tri-*O*-acetyl-1,6-anhydro-6-bromo-ß-D-galactopyranose (2.50 g, 8.7 mmol) in dry nitromethane (30 mL) was added dry $Hg(CN)_2$ (1.75 g, 8.7 mmol). A not quite clear solution resulted, and the reaction was complete in 2 h at room temperature (TLC, solvent A_1). The suspension was filtered through a bed of Celite, and the filtrate was concentrated to a small volume, diluted with dichloromethane (50 mL), washed with aq. 10 % KI (3 x 20 mL) then water (3 x 20 mL), dried over $MgSO_4$, and concentrated. Crystallization of the residue from ethanol gave the product (1.10 g, 65%), mp 93 °C, $[\alpha]_D^{21}$ -27.9° (*c* 1.0,chloroform); ^1H NMR ($CDCl_3$) δ 2.08, 2.12 (2 s, 6 H, $C\underline{H}_3CO$), 4.60 (m, 1 H, $J_{3,4}$= 0.2

Hz, $J_{3,5}$= 0.7 Hz, H-3), 4.70 (ddd, 1 H, $J_{5,6}$= 2.5 Hz, H-5), 4.93 (dd, 1 H, $J_{2,3}$= 4.3 Hz, H-2), 5.34 (d, 1 H, $J_{4,5}$= 0.2 Hz, H-4), 5.50 (t, 1 H, $J_{1,2}$= 1.4 Hz, H-1), 5.90 (d, 1 H, H-6); ^{13}C NMR ($CDCl_3$) δ 20.7, 20.8 (2C, $\underline{C}H_3CO$), 67.2 (C-2), 73.6 (C-4), 79.2 (C-3), 79.5 (C-5), 100.3 (C-1), 100.4 (C-6), 169.6, 169.9 (2 C, $CH_3\underline{C}O$).

Anal. Calcd for $C_{10}H_{12}O_7$: C, 49.18; H, 4.95. Found: C, 49.3 ; H, 5.2 .

Benzyl (2,3,4-Tri-O-acetyl-α-D-galactopyranosyl bromide) uronate (26). Lactone **14** (1.06 g, 3.5 mmol) was dissolved in 55% hydrogen bromide in glacial acid (25 mL) at O °C. After 50 h at room temperature (TLC, solvent A_1), chloroform (50 mL) was added, the organic phase was washed with water (3 x 20 mL), dried over $MgSO_4$, and concentrated. This material was used without further purification in subsequent experiments. A stirred solution of the residue in dry dichloromethane (20 mL) was treated dropwise with a solution of phenyl diazomethane[30] (708 mg, 6.0 mmol) in dichloromethane (8 mL). Stirring was continued for 1 h (TLC, solvent A_1) at ambient temperature. The excess of diazo compound was discharged by the addition of glacial acid, and the mixture was concentrated in vacuo to yield an oil. Chromatography of the residue on silica gel (solvent A_4) gave, after concentration of the appropriate fractions and drying of the residue under high vacuum, the title compound (0.70 g, 42% from **14**) as a foam, $[\alpha]_D^{22}$ +179.2° (*c* 0.55, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.82, 2.00, 2.10 (3 s, 9 H, $C\underline{H}_3CO$), 4.88 (d, 1 H, H-5), 5.06 (dd, 1 H, $J_{2,3}$= 10.6 Hz, H-2), 5.18 (dd, 2 H, J= 11.8 Hz, $C\underline{H}_2Ph$), 5.44 (dd, 1 H, $J_{3,4}$= 3.3 Hz, H-3), 5.82 (dd, 1H, $J_{4,5}$= 1.6 Hz, H-4), 6.76 (d, 1 H, $J_{1,2}$= 3.8 Hz, H-1), 7.37 (m, 5 H, $CH_2\underline{Ph}$); ^{13}C NMR ($CDCl_3$) δ 20.1, 20.5, 20.7 (3 C, $\underline{C}H_3CO$), 67.2, 67.6, 67.9, 72.4 (C-2, C-3, C-4, C-5), 67.9 ($\underline{C}H_2Ph$), 87.2 (C-1), 128.2, 128.7, 128.8, 129.0, 129.2 ($CH_2\underline{Ph}$), 165.1 (C-6), 169.4, 169.7, 169.9 (3 C, $CH_3\underline{C}O$).

Benzyl (Allyl 2,3,4-tri-O-acetyl-ß-D-galactopyranosid) uronate (27). A suspension of benzyl (2,3,4-tri-*O*-acetyl-α-D-galactopyranosyl bromide) uronate (**26**) (0.47 g, 1 mmol), Drierite (1 g), $Hg(CN)_2$ (130 mg, 0.5 mmol), and $HgBr_2$ (18 mg, 0.05 mmol) in dry allyl alcohol (5 mL) was stirred for 24 h at ambient temperature (TLC, solvent A_4). The mixture was concentrated in vacuo, diluted with chloroform (20 mL), and filtered. The filtrate was washed with aq. 10% KBr (3 x 5 mL) and water (2 x 5 mL), dried ($MgSO_4$), and concentrated. The crude material was purified by column chromatography (EtOAc gradient 9% - 17% in toluene) to yield **27** (0.33 g, 74%), $[\alpha]_D^{28}$ -9.6° (*c* 1.7, chloroform); ^{1}H NMR ($CDCl_3$) δ 1.85, 1.95, 2.05 (3 s, 9 H, $C\underline{H}_3CO$), 4.09, 4.39 (2 m, 2 H, $OCH_2CH{=}CH_2$), 4.31 (d, 1 H, H-5), 4.53 (d, 1H, $J_{1,2}$= 7.8 Hz, H-1), 5.16 (dd, 2 H, J= 11.8 Hz, $C\underline{H}_2Ph$) 5.18, 5.29, 5.84 (3

m, 3 H, $OCH_2CH=CH_2$), 5.24 (dd, 1 H, $J_{2,3}$= 10.4 Hz, H-2), 5.05 (dd, 1 H, $J_{3,4}$= 3.2 Hz, H-3), 5,69 (dd, 1 H, $J_{4,5}$= 1.3 Hz, H-4), 7.34 (m, $CH_2\underline{Ph}$); ^{13}C NMR ($CDCl_3$) δ 20.4, 20.6, 20.8 (3 C, $\underline{C}H_3CO$), 67.6 ($\underline{C}H_2Ph$), 68.3 (C-4), 68.5 (C-2), 69.7 ($\underline{C}H_2$-$CH=CH_2$), 70.6 (C-3), 72.3 (C-5), 99.8 (C-1), 117.4, 133.7 ($CH_2\underline{C}H=\underline{C}H_2$), 128.7, 128.8, 129.2, 134.9 ($CH2\underline{Ph}$), 166.5 (C-6), 169.3, 169.9, 170.0 (3 C, $CH_3\underline{C}O$).

3,4-Di-O-acetyl-ß-D-galactopyranurono-6,1-lactone (28). 2,3,4-Tri-*O*-acetyl-ß-D-galactopyranurono-6,1-lactone (**14**) (0.61 g, 2 mmol) in *N*,*N*-dimethylformamide (5 mL) and wheat germ lipase (0.10 g, No. L-3001 Sigma Chemical Co.) were added to K_2HPO_4 buffer (50 mL, pH 7), then the mixture was stirred at 25 °C. The reaction was monitored on TLC (solvent A_2). After 4 h, the reaction mixture was extracted with ethyl acetate, dried, and concentrated to give a syrupy residue, which was subjected to column chromatography on silica gel (solvent A_3) to afford **28** (0.10 g, 19%) as a syrup, $[\alpha]_D^{20}$ -5.2° (*c* 1.0, chloroform); ^1H NMR ($CDCl_3$) δ 2.08, 2.12 (2 s, 6 H, $C\underline{H}_3CO$), 4.03 (t, 1 H, H-2), 4.35 (t, 1 H, H-5), 5.42 (d, 2 H, $J_{4,5}$= 2.8 Hz, H-3, H-4), 5.83 (d, 1 H, $J_{1,2}$= 0.7 Hz, H-1); ^{13}C NMR ($CDCl_3$) δ 20.5 (2 C, $\underline{C}H_3CO$), 64.8, 68.1, 69.1, 69.9 (C-2, C-3, C-4, C-5), 102.4 (C-1), 168.9 (C-6), 169.3, 169.4 (2 C, $CH_3\underline{C}O$).

Anal. Calcd for $C_{10}H_{12}O_8$: C, 46.16; H, 4.65. Found: C, 46.2 ; H, 4.9.

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Fluoroorganic chemistry: synthetic challenges and biomedicinal rewards

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Asymmetric Reduction of 2-(*N*-Arylimino)-3,3,3-trifluoropropanoic Acid Esters Leading to Enantiomerically Enriched 3,3,3-Trifluoroalanine

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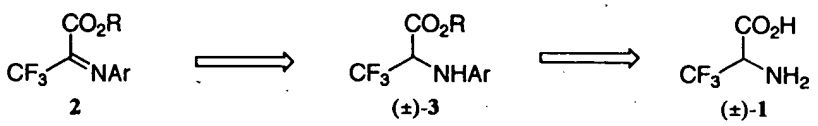
Abstract: Enantiomerically enriched 3,3,3-trifluoroalanine (**1**) (up to 62 % ee) has been synthesized by the asymmetric reduction of 2-(*N*-arylimino)-3,3,3-trifluoropropanoic acid esters with a chiral oxazaborolidine catalyst and subsequent oxidative removal of *N*-aromatic moiety with retention of the configuration. Detailed optimization studies revealed that the effects of solvents, temperature, and the structural modification of the substrate were drastic on the enantioselectivity. The absolute configuration of **1** was determined to be (*R*) by X-Ray crystallographic analysis of the corresponding *N*-(*S*)-(+)-camphorsulfonyl derivative.

Synthesis of fluorinated amino acids has been one of the current subjects owing to practical application to clarification of the physiological roles of specific enzymes.[1] Specifically, 3,3,3-trifluoroalanine **1** and its derivatives have received considerable attention because they act as suicide inhibitors for a number of pyridoxal enzymes.[2] A number of studies have been reported about the racemic trifluoroalanine **1**,[3] for example, *via* *N*-acyltrifluoroacetaldimines[3a,b] or a trifluoromethyloxazole intermediate.[3c,d] In contrast, studies on asymmetric synthesis of **1** are limited and the absolute configuration has not been clarified so far as known. In 1994, a patent by Kubota *et al.*[4] reported the attempt for chiral precursor of **1** through cyanation (Me_3SiCN) to *N*-[(*S*)-α-phenylethyl]-2,2,2-trifluoroacetaldimine, but with only 33 % de. Recently, a review by Kukhar[5] described that optically pure (>99% ee) **1** was successfully prepared by enzymatic resolution although the experimental and spectral details are not involved therein.

Our group recently reported a convenient route for racemic **1** by the reduction of 2-(*N*-arylimino)-3,3,3-trifluoropropanoic acid esters **2** with Zn-AcOH and subsequent oxidative removal of the aromatic moiety as shown in Scheme 1.[6] Here, we wish to report an asymmetric version of the process involving asymmetric reduction of the imine moiety of **2**.



Scheme 1

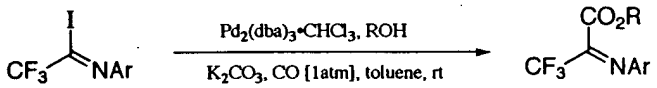
Meanwhile, asymmetric reduction of imine function to chiral amine is still a challenging subject to solve. Although wide range of studies have been devoted,[7] generally applicable methodologies have not been established. Especially, no enantioselective reduction of imines bearing two such highly electron-withdrawing groups (CO_2R and CF_3) like in the case of **2** have been examined, so that considerable difficulties

have been expected.

Asymmetric hydrogenations of imines have been attempted with a variety of chiral transition metal catalysts involving rhodium,[8] iridium,[9] and titanium.[10] High levels of enantioselectivity can be obtained for some specially substituted imine substrates such as *N*-acylhyrozones or cyclic imines. Similarly, oxazaboroines-$BHlid_3 \cdot THF$,[11] dialkoxyboranes,[12] and $NaBH_4$-$ZrCl_4$-chiral amino alcohols[13] have been used for reduction of imines and oximes. The ee value of the resulting amine of up to 90% ee was achieved in case of acetophenone *O*-methyloxime reduction with stoichiometric amounts of these chiral ligands. The reduction of aliphatic imines remain to afford low ee in general. Particularly, the ee decreased significantly when the reducing agent was used catalytically. Although Bolm *et al.*[14] described the use of catalytic amounts of β-hydroxy sulfoximine (10 mol %) in reduction of aromatic ketimines with $BH_3 \cdot SMe_2$, the best ee was up to 72%. Here, we examined the applicability of some reduction systems to our substrates **2** and present a full account of our studies of this reduction for the enantioselective synthesis of chiral 3,3,3-trifluoroalanine.[15] A detailed X-ray analysis for determination of the absolute configuration of 3,3,3-trifluoroalanine **1** was also described.

Results and discussion

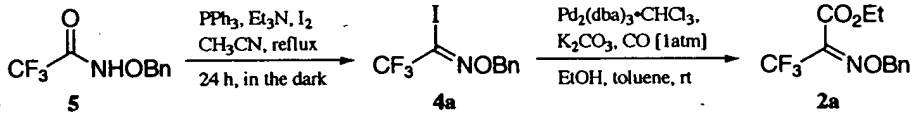
As summarized in Scheme 2, imino esters **2b-k** were prepared here by the previously reported method from our group.[6] In addition, oxime ether **2a** could be readily prepared in 77% yield in a similar way through carbonylation of iodide **4a** which derived from *N*-(benzyloxy)-2,2,2-trifluoroacetamide **5** (Scheme 3).



4b-k **2b-k**

b	R = Et, Ar = 2,6-$Me_2C_6H_3$	**g**	R = Et, Ar = *p*-$Me_2NC_6H_4$
c	R = Et, Ar = *m*-ClC_6H_4	**h**	R = Bn, Ar = *p*-$MeOC_6H_4$
d	R = Et, Ar = C_6H_5	**i**	R = (*L*)-menthyl, Ar = *p*-$MeOC_6H_4$
e	R = Et, Ar = *p*-MeC_6H_4	**j**	R = Bn, Ar = *p*-MeC_6H_4
f	R = Et, Ar = *p*-$MeOC_6H_4$	**k**	R = (*L*)-menthyl, Ar = *p*-MeC_6H_4

Scheme 2



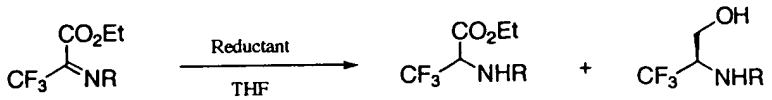
5 **4a** **2a**

Scheme 3

Considerable efforts have been paid to optimize the reaction conditions by examining the reductants, reaction temperature, solvents, and derivatization of substrates. Table 1 summarizes the results of the reduction of typical substrates **2a** and **2f** with a variety of reductants such as Itsuno's reagents (**A**[13] and **B**[11d]), Corey's reagents (**C**[16] and **E**[17]), and Pak's reagent (**D**).[18] The reductant **A** was used to reduce oxime ether **2a** and imino ester **2f**, but the reductant **A** was highly reactive enough to reduce both of imine and ester groups

to amino alcohols **6a** and **6f** in 94% and 95% yields, respectively (entry 1 and 2). $BH_3 \cdot THF$ is involved as a hydride source in the reductants **B-D** and catecholborane in **E**. Asymmetric reduction of imino ester **2f** using (*S*)-reductants **B-D** commonly gave amino ester (*S*)-**3f** together with amino alcohol (*R*)-**4f**, leaving the ee of the former below 32% (entry 3-5). One of the reasons of the lower ee(s) would be attributed to the formation of by-product (*R*)-**6f**, which also act as a ligand to give another *in situ*-formed oxazaborolizine and induce the formation of a counter enantiomer of (*S*)-**3f**. Use of reductant **E** with catecholborane could completely suppress such formation of amino alcohol (*R*)-**6f** and therefore improved the ee up to 63% with 93% yield (entry 6).

Table 1: Asymmetric Reduction of **2a** and **2f** with Reductants **A-E**



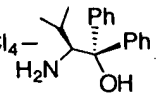
2a: R = OBn
2f: R = *p*-$MeOC_6H_4$

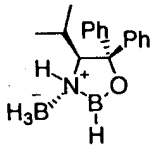
3f

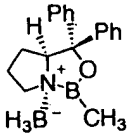
6a: R = H
6f: R = *p*-$MeOC_6H_4$

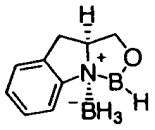
entry	substrate	reductant	temp. (°C)		yield (%)	ee (%)[a] (config.)		yield (%)	ee (%)[a] (config.)
1	**2a**	**A**	rt	-	0	-	**6a**	94	-
2	**2f**	**A**	rt	**3f**	0	-	**6f**	95	14 (*R*)
3	**2f**	**B**	-78~rt	**3f**	40	32 (*S*)	**6f**	56	46 (*R*)
4	**2f**	**C**	-78~rt	**3f**	42	28 (*S*)	**6f**	49	45 (*R*)
5	**2f**	**D**	-78~rt	**3f**	38	14 (*S*)	**6f**	45	11 (*R*)
6[b]	**2f**	**E**[c]	rt	**3f**	93	63 (*R*)	**6f**	-	-

[a] Determined by ^{19}F NMR of the MTPA ester of the corresponding amino alcohol. [b] The reduction was in CH_2Cl_2. [c] Catalytic amount of ligand was used (10 mol %).

A: $NaBH_4 - ZrCl_4 -$ 

B: 

C: 

D: 

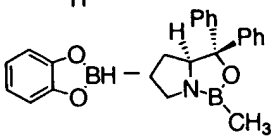
E: 

Table 2 shows a remarkable effect of the reaction temperature on enantioselectivity. The reduction of **2f** in CH_2Cl_2 was conducted at temperature ranging from -20 °C to 40 °C. The lower temperatures induced unexpectedly poor enantioselectivity, although Corey reported that the catecholborane procedure functions well for ketone at low temperature.[17] Upon raising the temperature, the enantioselectivities gradually improved, and ee of the product **3f** was raised up to 63% at 25 °C (room temperature). The negative effect of higher temperature at under reflux in CH_2Cl_2 was observed for this reduction. At this temperature range, the chemical yield was changed little. These results suggest that the complexation of the substrate with the

reductant may occur suitably at around 25 °C.

Table 2: Temperature Effect on the Reduction of **2f** with Reductant **E**. [a)]

entry	temp.(°C)	time (h)	yield of **3f** (%)	ee (%)
1	-20	36	90	25
2	0	24	88	37
3	25	20	93	63
4	30	20	91	60
5	reflux	18	80	12

[a)] CH_2Cl_2 as a solvent and 4Å molecular sieves were used in all reactions.

Then, the effect of the solvents such as hexane, aromatic compounds, THF, and halogenated hydrocarbons was examined by taking up the substrate **2f** (Table 3). Due to the poor solubility of oxazaborolidine, hexane was found to be unsuitable. Reduction in THF or $CHCl_3$ gave amino alcohol **3f** (15% yield) in addition (entry 4 and 7). In toluene, 89% yield and 43% ee were obtained as shown in entry 2. In terms of enantioselectivity, CH_2Cl_2 was the best choice of the solvent so far as examined. The yield and ee are 85% and 55%, respectively (entry 5 in Table 3). In particular, addition of 4Å molecular sieves markedly affected on the selectivity (63% ee in entry 6). Recently, it has been reported that trace of water in the reaction media lowers the ee from 95% to 50%.[19] The molecular sieves would be meaningful as a desiccant in this reduction system.

Table 3: Effect of Solvents on the Asymmetric Reduction of **2f** with the Reductant **E**.[a)]

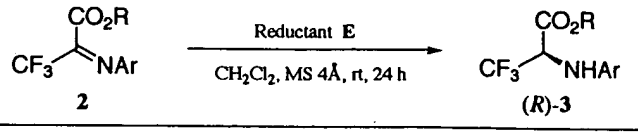
entry	solvent	time (h)	yield of **3f** (%)	ee (%)
1	Hexane	72	12[b)]	-
2	Toluene	28	89	43
3	Benzene	28	84	43
4[c)]	THF	18	72	40
5	CH_2Cl_2	24	85	55
6[d)]	CH_2Cl_2	20	93	63
7[c)]	$CHCl_3$	20	70	15

[a)] Reaction at 25 °C. [b)] The starting **2f** (82%) was recovered. [c)] Amino alcohol **6f** was obtained about 15% yield. [d)] 4Å molcular seives was used.

Adjust the structure of substrates to the catalyst is further examined by changing both ester and *N*-aryl moieties. A series of imino esters **2** containing (*L*)-menthyl ester **2i** and **2k** were also subjected to the reduction with reductant **E** and the results are summarized in Table 4. The reductant **E** was not effective for oxime ether **2a** and sterically hindered 2,6-dimethyl **2b**, recovering the substrates intact. The electronic effect of *N*-aryl group of **2** did not affect the selectivity. Thus, both electron withdrawing (*m*-chloro **2c**) and electron donating (*p*-methyl **2e** and *p*-methoxy **2f**) substituents gave the similar level of selectivities (entry 3-6). Substitution with more electron-donating substituent *p*-(*N*,*N*-dimethyl)amino group (**2g**) gave no reaction,

probably due to the substrate-catalyst complexation at *p*-NMe_2 nitrogen instead of at imine nitrogen. Then, the ethyl ester moiety of **2e** was changed to the bulkier benzyl (entry 10), which slightly improved the ee to 68% from 62%. The best selectivity (de) was obtained by using (*L*)-menthyl ester (71% de) as a result of double differentiation (entry 9).

Table 4: Asymmetric Reduction of the Imino Esters **2** with Reduction (*S*)-**E**



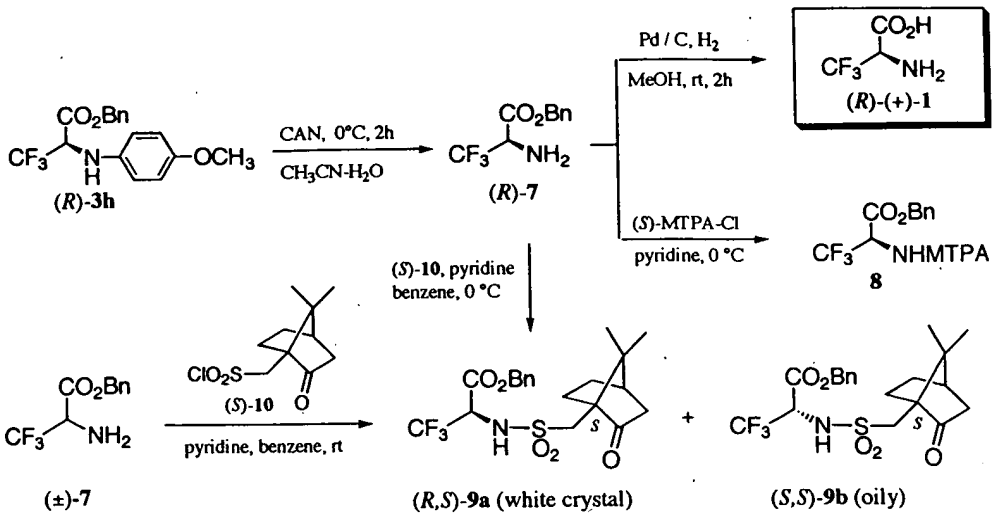
2 (*R*)-**3**

entry		R	Ar	yield of **3** (%)	ee (%)[a]	config.
1	**2a**	Et	BnO	0	-	
2	**2b**	Et	2,6-$Me_2C_6H_3$	0	-	
3	**2c**	Et	*m*-ClC_6H_4	94	63	*R*-(-)[b]
4	**2d**	Et	C_6H_5	93	61	*R*-(-)[b]
5	**2e**	Et	*p*-MeC_6H_4	90	62	*R*-(+)[b]
6	**2f**	Et	*p*-$MeOC_6H_4$	93	63	*R*-(-)[b]
7	**2g**	Et	*p*-$Me_2NC_6H_4$	0	-	
8	**2h**	Bn	*p*-$MeOC_6H_4$	91	62	*R*-(-)
9	**2i**	(*L*)-menthyl	*p*-$MeOC_6H_4$	>85	71[c]	*R*-(-)[b]
10	**2j**	Bn	*p*-MeC_6H_4	95	68	*R*-(+)[b]
11	**2k**	(*L*)-menthyl	*p*-MeC_6H_4	>85	68[c]	*R*-(+)[b]

[a] Determined by ^{19}F NMR of the MTPA ester of the corresponding amino alcohol ($LiAlH_4$). [b] Absolute configuration was assigned by comparison of ^{19}F NMR chemical shift of the MTPA esters of the corresponding amino alcohols. [c] Diastereomeric excess (de)

Further conversion to free 3,3,3-trifluoroalanine **1** was then accomplished. The amino ester **3j** (R = Bn, Ar = *p*-MeC_6H_4) was obtained as the sole crystal in this reaction. The optically pure (*R*)-**3j** was found to be available by recrystallization of **3j** (68% ee) from hexane.[20] However, oxidative removal of the *p*-methylphenyl moiety from **3j** to optically pure **1** was unsuccessful. The removal of the *p*-methoxyphenyl moiety from (*R*)-**3h** (R = Bn, Ar = *p*-$MeOC_6H_4$) by treatment with cerium (IV) diammonium nitrate at 0 °C in CH_3CN-H_2O[21] afforded the corresponding optically active amine derivative (*R*)-**7** in 87% yield with retention of the optical purity of (62% ee), which was confirmed by ^{19}F NMR analysis of the MTPA amide **8**; a couple of peaks in ^{19}F NMR was observed at d 92.75 ppm [(*R*), 81%] and 92.56 ppm [(*S*), 19%) for CF_3 on the MTPA part. A simple treatment of (*R*)-**7** with Pd / C catalyst under hydrogen atmosphere led to (*R*)-(+)-3,3,3-trifluoroalanine **1** (62% ee, 90% yield) ($[\alpha]_D^{23}$ + 6.8, *c* 0.76, MeOH) as a free amine form. The optical purity was confirmed further by HPLC analysis.

The absolute configuration of amino ester **3h** was confirmed by X-ray crystallographic analysis of *N*-(*S*)-(+)-camphorsulfonyl derivative (*R*,*S*)-**9a** which was prepared by resolution of racemic amide **9a,b**. Thus,



Scheme 4

the racemic amine **7** prepared from racemic **3h** was allowed to react with (*S*)-(+)-10-camphorsulfonyl chloride to give a 1:1 diasteromeric mixture of (*R,S*)-**9a** and (*S,S*)-**9b**, which were separated by HPLC to provide a crystalline (*R,S*)-**9a** and an oily (*S,S*)-**9b**. The former (*R,S*)-**9a** was recrystallized from ethyl acetate-hexane (1 : 5) to yield a white needle suitable for X-Ray analysis. An arbitrary view of (*R, S*)-**9a** is shown in Figure 1 with appropriate atomic labeling.

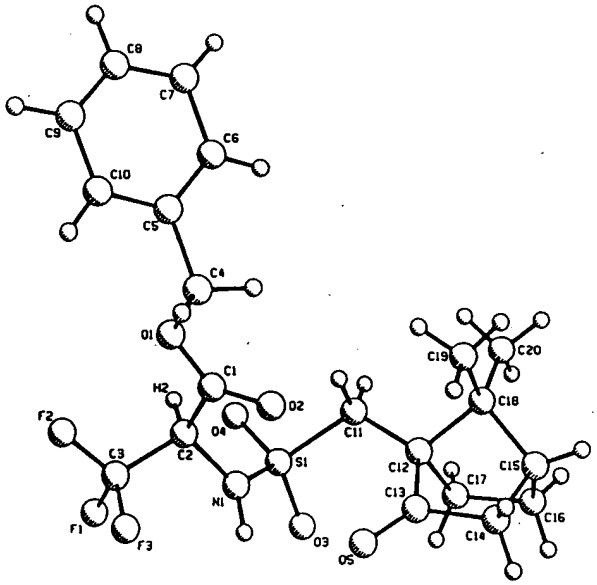
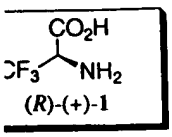
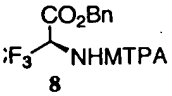


Figure 1. X-Ray Crystallographic Data of (*R,S*)-**9a**.



(*R*)-(+)-**1**



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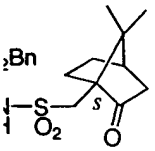

9b (oily)

mphorsulfonyl chloride
by HPLC to provide a
om ethyl acetate-hexane
)-**9a** is shown in Figure

The absolute configuration of the reduction product **3h** was thus assigned to be (*R*) by conversion to the camphorsulfonyl derivative (*R,S*)-**9a** and the comparison of ^{19}F or ^{1}H NMR chemical shifts with both of (*R,S*)-**9a** and (*S,S*)-**9b**.

Experimental Section

General. Melting points were measured on a capillary apparatus and are uncorrected. Infrared spectra (IR) were measured on Hitachi Model 270-30 Infrared Spectrophotometer. ^{1}H (200 MHz), and ^{19}F (188 MHz) NMR spectra were recorded by Varian VXR 200 NMR apparatus in $CDCl_3$ or D_2O as indicated and the chemical shifts are reported in δ (ppm) values downfield from TMS (^{1}H NMR) or C_6F_6 (^{19}F NMR), respectively, as internal standards. Optical rotation was measured at 23 °C in a cell with 50 mm length and 1 mL capacity using a Horiba High Sensitive Polarimeter SEPA-300. Elemental analyses were performed on Perkin Elmer series II CHNS/O Analyzer 2400.

Hexane, THF, toluene, and benzene were distilled from sodium-benzophenone ketyl under nitrogen. Methylene chloride (CH_2Cl_2) and chloroform ($CHCl_3$) were distilled from CaH_2. Catecholborane was distilled under reduced pressure (70 °C / 100 mmHg) and stored as 2 M CH_2Cl_2 or toluene. In all other cases, commercially available reagent grade solvents were employed without further purification. (*S*)-(+)-2-Amino-3-methyl-1,1-diphenylbutanol was prepared by the known method.[11d] (*S*)-2-Indoline carboxylic acid and (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine were purchased from TCI Tokyo Kasei Kogyo Co., ltd. (Tokyo). (*S*)-(+)-Methoxy-α-(trifluoromethyl)phenylacetic acid (MTPA) was obtained from the same source and converted to the acid chloride (MTPA-Cl) using the Mosher's procedure.[22]

Preparation of 2-(*N*-Arylimino)-3,3,3-trifluoropropanoates 2b-k. The compounds **2b**, **2d-f**, **2h**, and **2j** were prepared according to the procedure reported previously from our group.[6] Other imino esters **2c**, **2g**, **2i**, and **2k** were prepared in 30-80% yields from the corresponding imidoyl iodides **4** in a similar way and the spectral data are shown in the following. The spectral data suggest that imino esters **2b-k** have a single geometry (*E* or *Z*), however, which could not be assigned so far.

Ethyl 2-[*N*-(*p*-Chlorophenyl)imino]-3,3,3-trifluoropropanoate 2c: 80% yield; IR (neat) 1746, 1682, 858, 784, 688 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.12 (t, *J* = 7.2 Hz, 3H, CH_3), 4.22 (q, *J* = 7.2 Hz, 2H, CH_2), 6.79-6.98 (m, 2H, H_{arom}), 7.19-7.35 (m, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 91.87 (s, CF_3). Anal. Calcd for $C_{11}H_9ClF_3NO_2$: C, 47.25; H, 3.24; N, 5.01. Found: C, 47.19; H, 3.52; N, 5.18.

Ethyl 2-{*N*-[*p*-(*N,N*-Dimethylamino)phenyl]imino}-3,3,3-trifluoropropanoate 2g: 58% yield; IR (neat) 1738, 1582, 818 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.18 (t, *J* = 7.1 Hz, 6H, CH_3), 1.27 (t, *J* = 7.1 Hz, 3H, CH_3), 3.38 (q, *J* = 7.0 Hz, 4H, CH_2), 4.33 (q, *J* = 7.0 Hz, 2H, CH_2), 6.60 (d, *J* = 8.9 Hz, 2H, H_{arom}), 7.08 (d, *J* = 8.9 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 92.05 (s, CF_3). Anal. Calcd for $C_{15}H_{19}F_3N_2O_2$: C, 56.96; H, 6.05; N, 8.86. Found: C, 56.50; H, 6.48; N, 8.71.

(*L*)-Menthyl 2-[*N*-(*p*-Anisyl)imino]-3,3,3-trifluoropropanoate 2i: 35% yield; IR (neat) 1736, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.62 (t, *J* = 6.9 Hz, 3H, CH_3), 0.78 (t, *J* = 7.0 Hz, 3H, CH_3), 0.88 (t, *J* = 6.2 Hz, 3H, CH_3), 0.70-1.97 (m, 9H, $H_{menthyl}$), 3.82 (s, 3H, OCH_3), 4.76 (td, *J* = 7.1 Hz, *J* = 4.4 Hz, 1H, OCH), 6.88 (d, *J* = 9.1 Hz, 2H, H_{arom}), 7.01 (d, *J* = 8.8 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 92.15 (s,

CF_3). Anal. Calcd for $C_{20}H_{26}F_3NO_3$: C, 62.23; H, 6.80; N, 3.63. Found: C, 62.23; H, 6.67; N, 3.89.

(*L*)-Menthyl 2-[*N*-(*p*-Tolyl)imino]-3,3,3-trifluoropropanoate 2k: 32% yield; IR (neat) 1736, 1662 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.58 (t, J = 6.7 Hz, 3H, CH_3), 0.75 (t, J = 6.8 Hz, 3H, CH_3), 0.86 (t, J = 6.5 Hz, 3H, CH_3), 0.75-1.90 (m, 9H, $H_{menthyl}$), 2.35 (s, 3H, CH_3), 4.72 (td, J = 10.7 Hz, J = 4.4 Hz, 1H, OCH), 6.87 (d, J = 8.3 Hz, 2H, H_{arom}), 7.01 (d, J = 8.1 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 91.97 (s, CF_3). Anal. Calcd for $C_{20}H_{26}F_3NO_2$: C, 65.02; H, 7.09; N, 3.79. Found: C, 64.86; H, 7.08; N, 4.15.

***N*-(Benzyloxy)-2,2,2-trifluoroacetimidoyl Iodide 4a.** To a mixture of PPh_3 (3.6 g, 13.7 mmol) and *N*-(benzyloxy)-2,2,2-trifluoroacetamide **5** (2.0 g, 9.1 mmol) (prepared from trifluoroacetic anhydride and the *O*-benzylhydroxylamine)[23] in dry acetonitrile (15 mL) was added iodine (2.8 g, 10.9 mmol) and Et_3N (1.1 g, 10.9 mmol) at 0 °C in the dark. After warming to room temperature, the contents were stirred for 24 h. The solvent was removed under reduced pressure. The residue was diluted with hexane and the crystalline material formed was removed by filtration. The usual workup and subsequent purification by silica gel column chromatography (hexane) gave iodide **4a** (2.5 g, 83% yield) as a colorless oil: IR (neat) 1590 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.41 (s, 2H, CH_2), 7.38 (s, 5H, C_6H_5); ^{19}F ($CDCl_3$) δ 96.21 (s, CF_3). Anal. Calcd for $C_9H_7F_3INO$: C, 32.85; H, 2.14; N, 4.26. Found: C, 32.62; H, 2.21; N, 4.29.

Ethyl 2-(*N*-Benzyloxyimino)-3,3,3-trifluoropropanoate 2a. A two-necked flask with a septum cap and a condenser topped with CO (1 atm.) inlet was charged with $Pd_2(dba)_3 \cdot CHCl_3$[24] (0.16 g, 0.15 mmol) and K_2CO_3 (0.84 g, 6.0 mmol). Then, trifluoroacetimidoyl iodide **4a** (1.0 g, 3.0 mmol) in toluene (10 mL) and EtOH (0.36 mL, 6.0 mmol) were added through a syringe. The mixture was stirred at room temperature for 20 h and passed through a short florisil column (hexane). Concentration followed by purification through silica gel column chromatography with ethyl acetate-hexane (1 : 50) gave **2a** (0.64 g, 77% yield) as a colorless oil: IR (neat) 1750, 1632 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.1 Hz, 3H, CH_3), 4.36 (q, J = 7.1 Hz, 2H, CH_2), 5.30 (s, 2H, CH_2), 7.36 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 95.96 (s, CF_3). Anal. Calcd for $C_{12}H_{12}F_3NO_3$: C, 52.37; H, 4.39; N, 5.09. Found: C, 52.44; H, 4.45; N, 5.10.

Asymmetric Reduction of 2a Using Reductant A.[13] To a suspension of $ZrCl_4$ (127 mg, 0.54 mmol) in THF (1.0 mL) was added $NaBH_4$ (82.5 mg, 2.18 mmol) at room temperature under nitrogen. After the mixture had been stirred for 20 h, a solution of (*S*)-(+)-2-amino-3-methyl-1,1-diphenylbutanol (92.7 mg, 0.36 mmol) in THF (1.0 mL) was added at room temperature and the mixture was stirred for a further 20 h. To the resulting chiral reductant **A** was added **2a** (100 mg, 0.36 mmol) and the mixture was stirred for 1 h at room temperature. Work up gave amino alcohol **6a** which was isolated its acetate form in 94% yield (44 mg) as a colorless oil. ^1H NMR ($CDCl_3$) δ 2.09 (s, 3H, CH_3), 2.11 (s, 3H, CH_3), 4.16-4.49 (m, 2H, CH_2), 4.82-5.29 (m, 1H, CH), 5.89-5.99 (br, 1H, NH); ^{19}F NMR ($CDCl_3$) δ 87.84 (d, J = 7.6 Hz, CF_3).

Asymmetric Reduction of 2f Using Reductant B.[11d] A solution of borane (1 M in THF, 0.81 mL, 0.81 mmol) was added dropwise to (*S*)-(+)-2-Amino-3-methyl-1,1-diphenylbutanol (103 mg, 0.40 mmol) in THF (1.0 mL) at -78 °C. The solution was gradually warmed to 0 °C and stirred for 8 h. Imino ester **2f** (100 mg, 0.36 mmol) in THF (1.0 mL) was added at -78 °C. The mixture was gradually warmed to

room temperature and stirring was continued at room temperature for 1 h. Then water was added and the mixture was extracted with ethyl acetate (3 × 5 mL). The combined organic extracts were washed with brine, dried (magnesium sulfate), and concentrated. Chromatography of the residue on silica gel afforded amino ester **3f** (40 mg, 40% yield) and amino alcohol **6f** (47.8 mg, 56% yield) as colorless oils.

Ethyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3f: 32% ee, $[\alpha]_D^{23}$ -11.4 (*c* 0.12, $CHCl_3$); IR (neat) 3396, 1748, 1518, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 3.76 (s, 3H, OCH_3), 4.19-4.40 (m, 2H, OCH_2), 4.44 (q, *J* = 6.9 Hz, 1H, CH), 6.70 (d, *J* = 9.1 Hz, 2H, H_{arom}), 6.81 (d, *J* = 9.1 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.06 (d, *J* = 6.4 Hz, CF_3). Anal. Calcd for $C_{12}H_{14}F_3NO_3$: C, 51.99; H, 5.09; N, 5.05. Found: C, 52.15; H, 5.32; N, 5.15.

2-[*N*-(*p*-Anisyl)amino]-3,3,3-trifluoropropanol 6f: IR (neat) 3404, 1516, 824 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3H, OCH_3), 3.79-3.97(m, 3H, $CHCH_2$), 6.71 (d, *J* = 9.2 Hz, 2H, H_{arom}), 6.81 (d, *J* = 9.0 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 88.08 (d, *J* = 6.1 Hz, CF_3). Anal. Calcd for $C_{10}H_{12}F_3NO_2$: C, 51.07; H, 5.14; N, 5.96. Found: C, 50.74; H, 5.01; N, 6.20.

Asymmetric Reduction of 2f with Reductants C[16] and D.[18] A similar procedure to the above experiment with reductant **B** was used.

A Typical Procedure for the Asymmetric Reduction of Imino Esters 2 with Reductant E. To a solution of imino ester **2** (0.20 mmol), (*S*)-5,5-diphenyl-2-methyl-3,4-propano-1,3,2-oxazaborolidine (0.02 mmol), and 4Å molecular sieves in CH_2Cl_2 (1 mL) at room temperature was added catecholborane (2 M in CH_2Cl_2, 0.40 mmol) under nitrogen. After being stirred for 24 h, the reaction was quenched by addition of water and the organic layer was extracted with hexane. Usual workup followed by column chromatographic purification on silica gel with 10% benzene in hexane gave **3**.

(*R*)-(-)-Ethyl 2-[*N*-(*m*-Chlorophenyl)amino]-3,3,3-trifluoropropanoate 3c: 63% ee; $[\alpha]_D^{23}$ -22.86 (*c* 0.41, $CHCl_3$); IR (neat) 3412, 1748, 1604, 854, 770, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (t, *J* = 7.0 Hz, 3H, CH_3), 4.22-4.45 (m, 2H, CH_2), 4.51-4.71 (m, 2H, CHNH), 6.56-6.88 (m, 3H, H_{arom}), 7.08-7.18 (m, 1H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.23 (d, *J* = 7.0 Hz, CF_3). Anal. Calcd for $C_{11}H_{11}ClF_3NO_2$: C, 46.92; H, 3.94; N, 4.97. Found: C, 46.92; H, 4.02; N, 5.06.

(*R*)-(-)-Ethyl 2-(*N*-Phenylamino)-3,3,3-trifluoropropanoate 3d: 61% ee; $[\alpha]_D^{23}$ -34.60 (*c* 0.41, $CHCl_3$); IR (neat) 3416, 1750, 1608, 750, 682 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (t, *J* = 7.1 Hz, 3H, CH_3), 4.20-4.43 (m, 2H, CH_2), 4.49-4.68 (m, 2H, CHNH), 6.68-6.90 (m, 3H, H_{arom}), 7.17-7.27 (m, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.10 (d, *J* = 5.8 Hz, CF_3). Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.89; N, 5.67. Found: C, 53.45; H, 4.99; N, 5.72.

(*R*)-(+)-Ethyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3e: 62% ee; $[\alpha]_D^{23}$ +86.16 (*c* 0.10, $CHCl_3$); IR (neat) 3412, 1750, 1622, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31 (t, *J* = 7.2 Hz, 3H, CH_3), 4.18-4.38 (m, 2H, CH_2), 4.40-4.62 (m, 2H, CHNH), 6.64 (d, *J* = 8.4 Hz, 2H, H_{arom}), 7.03 (d, *J* = 8.1 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.11 (d, *J* = 6.8 Hz, CF_3). Anal. Calcd for $C_{12}H_{14}F_3NO_2$: C, 55.17; H, 5.40; N, 5.36. Found: C, 55.32; H, 5.48; N, 5.29.

(*R*)-(-)-Benzyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3h: 62% ee; $[\alpha]_D^{23}$ -6.41 (*c* 0.30, $CHCl_3$); IR (neat) 3400, 1748, 1598, 822, 748, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.68 (s, 3H, OCH_3), 4.23 (d,

J = 9.3 Hz, 1H, NH), 4.36-4.53 (m, 1H, CH), 5.18 (s, 2H, CH_2), 6.61 (d, *J* = 9.1 Hz, 2H, H_{arom}), 6.72 (d, *J* = 9.2 Hz, 2H, H_{arom}) 7.28 (m, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.22 (d, *J* = 6.8 Hz, CF_3). Anal. Calcd for $C_{17}H_{16}F_3NO_3$: C, 60.18; H, 4.75; N, 4.13. Found: C, 59.80; H, 5.09; N, 4.08.

(*R*)-(-)-(*L*)-Menthyl 2-[*N*-(*p*-Anisyl)]-3,3,3-trifluoropropanoate 3i: 71% ee; $[\alpha]_D^{23}$ -78.90 (*c* 0.10, $CHCl_3$); IR (neat) 3400, 1742, 1518, 822 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (t, *J* = 7.0 Hz, 3H, CH_3), 0.85 (t, *J* = 7.0 Hz, 3H, CH_3), 0.91 (t, *J* = 6.5 Hz, 3H, CH_3), 0.74-2.05 (m, 9H, $H_{menthyl}$), 3.76 (s, 3H, OCH_3), 4.44 (q, J = 6,8 Hz, 1H, $CHCF_3$), 4.80 (td, *J* = 11.0 Hz, *J* = 4.5 Hz, 1H, CH), 6.70 (d, *J* = 9.2 Hz, 2H, H_{arom}), 6.81 (d, *J* = 9.2 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.23 (d, *J* = 6.8 Hz, CF_3). Anal. Calcd for $C_{20}H_{28}F_3NO_3$: C, 62.00; H, 7.28; N, 3.62. Found: C, 62.01; H, 7.68; N, 3.61.

(*R*)-(+)-Benzyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3j: 68% ee; $[\alpha]_D^{23}$ +13.24 (*c* 0.20, $CHCl_3$); IR (neat) 3400, 1738, 1622, 810, 726, 698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H, CH_3), 4.39 (br, 1H, NH), 4.52-4.65 (m, 1H, $CHCF_3$), 5.26 (s, 2H, CH_2),), 6.63 (d, *J* = 8.4 Hz, 2H, H_{arom}), 6.72 (d, *J* = 8.1 Hz, 2H, H_{arom}) 7.35 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.11 (d, *J* = 6.8 Hz, CF_3). Anal. Calcd for $C_{17}H_{16}F_3NO_2$: C, 63.15; H, 4.99; N, 4.33. Found: C,63.14; H, 5.18; N, 4.26.

(*R*)-(+)-(*L*)-Menthyl 3,3,3-Trifluoro-2-[*N*-(*p*-tolyl)]propanoate 3k: 68% ee; $[\alpha]_D^{23}$ +109.6 (*c* 0.15, $CHCl_3$); IR (neat) 3412, 1748, 1604, 810 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (t, *J* = 6.9 Hz, 3H, CH_3), 0.86 (t, *J* = 7.0 Hz, 3H, CH_3), 0.91 (t, *J* = 6.6 Hz, 3H, CH_3), 0.80-2.05 (m, 9H, $H_{menthyl}$), 2.26 (s, 3H, CH_3), 4.40-4.62 (m, 2H, CHNH), 4.62 (td, *J* = 10.9 Hz, *J* = 4.5 Hz, 1H, CH),), 6.65 (d, *J* = 8.5 Hz, 2H, H_{arom}), 7.04 (d, *J* = 8.8 Hz, 2H, H_{arom}); ^{19}F NMR ($CDCl_3$) δ 89.31 (d, *J* = 6.2 Hz, CF_3). Anal. Calcd for $C_{20}H_{28}F_3NO_2$: C, 64.67; H, 7.60; N, 3.77. Found: C, 64.32; H, 7.50; N, 4.22.

Determination of Enantiomeric Excess for Amino Esters 3. ***Typical procedure.*** Amino ester **3c** (10 mg, 0.036 mmol) in THF (1.0 mL) was added dropwise to a solution of $LiAlH_4$ (4.0 mg, 0.11 mmol) in THF (1.0 mL) at 0 °C, and the mixture was stirred for 0.5 h. The reaction was quenched by addition of water and the organic layer was extracted with ethyl acetate. The extract was washed with brine and dried (magnesium sulfate). Upon removal of the solvent, to the residue (crude amino alcohol **6c**) in benzene (1.0 mL) was directly added (*S*)-(-)-MTPA-Cl (14 mg, 0.055 mmol) and pyridine (14 mg, 0.18 mmol). Usual workup followed by ^{19}F NMR analysis of the resulting MTPA ester. ^{19}F NMR spectrum of the MTPA ester showed two doublets for CF_3 at δ 87.52 (d, *J* = 5.9 Hz) [(*R*), 81.5%] and 87.67 ppm (d, *J* = 5.9 Hz) [(*S*), 18.5%). Enantiomeric excess of other amino esters were determined by a similar method and the ^{19}F NMR spectral data are shown in the following: **3d**: δ 87.49 (d, *J* = 6.2 Hz) [(*R*), 81.5%], 87.67 (d, *J* = 6.6 Hz) [(*S*), 18.5%]; **3e**: δ 87.54 (d, *J* = 6.6 Hz) [(*R*), 81%], 87.72 (d, *J* = 7.0 Hz) [(*S*), 19%]; **3f**: δ 87.55 (d, *J* = 6.8 Hz) [(*R*), 81.5%], 87.74 (d, *J* = 6.9 Hz) [(*S*), 18.5%]; **3h**: δ 87.55 (d, *J* = 6.8 Hz) [(*R*), 81%], 87.74 (d, *J* = 6.9 Hz) [(*S*), 19%]; **3i**: δ 87.55 (d, *J* = 6.8 Hz) [(*R*), 85.5%], 87.74 (d, *J* = 6.9 Hz) [(*S*), 14.5 %]; **3j**: δ 87.54 (d, *J* = 6.6 Hz) [(*R*), 84%], 87.72 (d, *J* = 7.0 Hz) [(*S*), 16%]; **3k**: δ 87.54 (d, *J* = 6.6 Hz) [(*R*), 84%], 87.72 (d, *J* = 7.0 Hz) [(*S*), 16%].

(*R*)-(+)-Benzyl 2-Amino-3,3,3-trifluoropropanoate 7. A solution of (*R*)-**3h** (0.2 g, 0.58 mmol) in CH_3CN (20 mL) was added to cerium ammonium nitrate (0.96 g, 1.76 mmol) in water (6.8 mL) at 0 °C over a period of 10 minutes and the whole was stirred for additional 2 h. After addition of water, the

mixture was extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulfate. Concentration followed by purification through silica gel column chromatography with hexane-ethyl acetate (3 : 1) gave (*R*)-(+)-**7** (0.12 g, 87% yield) as colorless oil: $[\alpha]_D^{23}$ + 4.81, (*c* 0.12, MeOH). IR (neat) 3432, 1752, 1616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.90 (s, 2H, NH_2), 4.15 (q, *J* = 7.3 Hz, 1H, CH), 5.26 (s, 2H, CH_2), 7.37 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 86.92 (d, *J* = 7.3 Hz, CF_3). Anal. Calcd for $C_{10}H_{10}F_3NO_2$: C, 51.51; H, 4.32; N, 6.01. Found: C, 51.38; H, 4.79; N, 5.98.

Synthesis of Diastereomeric Mixture of Benzyl 2-(*N*-Camphorsulfonylamino)-3,3,3-trifluoropropanoate 9a and 9b. To a solution of racemic **7** (0.1 g, 0.43 mmol) and (*S*)-(+)-camphorsulfonyl chloride (0.32 g, 1.28 mmol) in benzene (2.0 mL) was added pyridine (0.34 g, 4.28 mmol) at room temperature. After the solution was stirred for 2 h, the reaction was quenched by addition of 10% aq. HCl and the organic layer was extracted with ethyl acetate. Usual workup followed by column chromatographic purification on silica gel (ethyl acetate : hexane = 1 : 3) gave a mixture of diastereomers **9a** and **9b** (1 : 1) which were separated by HPLC using LiChrosorb Si 60 (7 μm) (ethyl acetate : hexane = 1 : 5; Flow rate = 2.0 ml / min) gave optically pure (*R,S*)-**9a** (white crystal) (48 min) and (*S, S*)-**9b** (oily) (44 min).

Compound (*R,S*)-(+)-**9a**: mp: 101-101.5 °C; $[\alpha]_D^{23}$ +6.04 (*c* 0.79, $CHCl_3$); IR (CH_2Cl_2) 1752, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.86 (s, 3H, CH_3), 0.98 (s, 3H, CH_3), 1.23-2.52 (m, 7H, $H_{camphor}$), 3.02, 3.43 (AB, *J* = 14.2 Hz, 2H, CH_2), 4.78-4.95 (m, 1H, CH), 5.30 (s, 2H, CH_2), 6.99 (d, *J* = 9.14 Hz, 1H, NH), 7.34 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.77 (d, *J* = 7.3 Hz, CF_3). Anal. Calcd for $C_{20}H_{24}F_3NO_5S$: C, 53.68; H, 5.41; N, 3.13. Found: C, 53.34; H, 5.56; N, 3.36.

Compound (*S,S*)-(-)-**9b**: $[\alpha]_D^{23}$ -6.01 (*c* 0.94, $CHCl_3$); IR (CH_2Cl_2) 3284, 1752, 1738 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 1.24-2.54 (m, 7H, $H_{camphor}$), 3.08, 3.50 (AB, *J* = 14.2 Hz, 2H, CH_2), 4.82-4.99 (m, 1H, CH), 5.30 (s, 2H, CH_2), 6.53 (d, *J* = 9.14 Hz, 1H, NH), 7.37 (s, 5H, C_6H_5); ^{19}F NMR ($CDCl_3$) δ 89.66 (d, *J* = 7.0 Hz, CF_3). Anal. Calcd for $C_{20}H_{24}F_3NO_5S$: C, 53.68; H, 5.41; N, 3.13. Found: C, 53.52; H, 5.58; N, 3.40.

(*R*)-(+)-3,3,3-Trifluoroalanine 1: To a suspension of 5% Pd / C (0.05 g, 0.02 mmol) in methanol (2 mL) was added (*R*)-**7** (0.1 g, 0.43 mmol) in methanol. The mixture was stirred under an atmosphere of hydrogen for 1 h and passed through florisil column. The filtrate was evaporated to give a white crystal (*R*)-(+)-**1** (0.06 g, 90% yield), $[\alpha]_D^{23}$ + 6.89 (*c* 0.76, MeOH), (decomp. above 210 °C): ^1H NMR (D_2O) δ 4.47 (q, *J* = 8.3 Hz, 1H, CF_3CH), 4.75 (s, 3H, NH_3^+); ^{19}F NMR (D_2O) δ 91.32 (d, *J* = 8.5 Hz, CF_3). Anal. Calcd for $C_3H_4F_3NO_2$: C, 25.19; H, 2.82; N, 9.79. Found: C, 25.37; H, 2.97; N, 9.72. Attempts for raising the % ee by recrystallization from several solvent system were unsuccessful.

The optical purity (62% ee) was determined by HPLC analysis using SUMICHIRAL OA-5000 (1 mM aqueous $CuSO_4$; Flow rate = 1.0 mL / min; UV Detector 254 nm), which showed a couple of peaks at 12.0 min (81%) and 24.0 min (19%).

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Gold(I)-Catalyzed Asymmetric Aldol Reactions of Isocyanoacetic Acid Derivatives with Fluoroaryl Aldehydes

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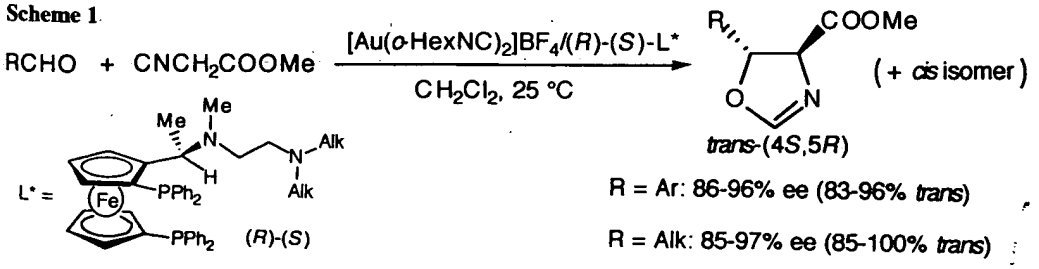
Abstract: The catalytic asymmetric synthesis of stereochemically defined fluoro-phenylserines is reported. In the title reaction, when methyl isocyanoacetate is employed, the number of fluorine atoms in the phenyl ring of benzaldehyde controls stereochemical outcome of the reaction giving rise in the case of monofluorobenzaldehydes corresponding *trans*-oxazolines with more than 90% of both *trans*-selectivity and % ee, while in the case of polyfluorobenzaldehydes corresponding *cis*-oxazolines are formed as dominant isomers with high enantiomeric excess (up to 63% of *cis* with 86-90% ee). In contrast to this, aldol reactions of isocyanoacetamide with fluoro-benzaldehydes provide dominant formation of *trans*-oxazolines (77-92% of *trans* with 80-94% ee) in all cases studied. The observed unusual stereodifferentiation in the reaction of methyl isocyanoacetate with polyfluorobenzaldehydes is rationalized on the basis of an electron donor—acceptor type attractive interaction between the polyfluorophenyl ring and the enolate oxygen.

INTRODUCTION

Owing to the general awareness of the effects that stereochemistry may have on a chiral compound biological activity, metabolism, and disposition,[2] the development of EPC synthesis[3] is today a topic of fundamental importance.[4] The efficient asymmetric approaches, allowing to achieve levels of stereoselectivity that rival enzymatic systems, have been developed for many classes of organic compounds. By contrast, fluoro-organic compounds turned out to be difficult targets for EPC synthesis. Now it is commonly recognized, that fluorine can dramatically alter both the course and stereochemical outcome of the reactions established for hydrocarbon patterns thus providing a challenge to the asymmetric synthesis of fluorinated compounds.[5] With the growing importance of enantiomerically pure fluoro-organic compounds in the pharmaceutical, agrochemical and optoelectronic industries, stereocontrolled preparation of fluorine-containing compounds has received much attention recently.[6] Methods to achieve this aim, wherein truly catalytic amount of an asymmetric agent is required, represent the most desirable solutions.[7] In the recent communications[1] we have demonstrated that the gold(I)-catalyzed asymmetric aldol reaction[8] (Scheme 1) provides an effective, synthetically useful approach to the series of fluoro-phenylserines of high diastereo- and enantiomeric purity. In this paper we report full details of our investigations which, apart from synthetic results, have revealed surprising dependence of stereochemical outcome of the asymmetric aldol reactions upon the number of fluorine atoms in the phenyl ring of starting benzaldehyde and the nature of isocyanoacetic acid derivative used as well.

Scheme 1



RESULTS AND DISCUSSION

Gold(I)-catalyzed asymmetric aldol reaction consists in the interaction between an aldehyde and methyl isocyanoacetate,[9] catalyzed by 1-2 mol % of gold(I) complex co-ordinated with chiral *N,N,N',N'*-tetra-alkylethylenediamino-substituted bis(diphenylphosphino)ferrocene ligand, leading to the optically active *trans*-5-substituted-2-oxazoline-4-carboxylates[10] with high enantio- and diastereoselectivity (Scheme 1).[8] Desirable *syn*-(2*S*)-β-(substituted)serines can be easily released from the corresponding diastereo- and enantiomerically pure *trans*-oxazolines under the standard conditions of acidic hydrolysis. External chiral ferrocenylphosphine ligands used in this reaction, differing for *N,N*-dialkylamino group at the terminal position of the pendent side chain, are commercially available or can be readily prepared with high overall yield and even in the ten-grams scale by well established 7-steps procedure starting with commercial ferrocene.[8b,h,11] Previous extensive studies on the gold(I)-catalyzed asymmetric aldol reaction have demonstrated its generality for the asymmetric synthesis of various β-(substituted)serines and other natural products[12] as well as its preparative advantage over stoichiometric versions of asymmetric aldol reaction.[13] However, despite the general applicability of this reaction to the wide range of alkyl, alkenyl, and aryl aldehydes its stereochemical outcome is not always unambiguous, varying from the excellent (100% de, 97% ee, R = *tert*-Bu)[8a,h] to poor (50% de, 6% ee, R = 2-C_5H_4N)[8i] depending on the nature of aldehyde used. Behavior of fluoroaryl aldehydes under the conditions of the gold(I)-catalyzed asymmetric aldol reaction was not previously studied. Therefore, the lure of a general asymmetric synthesis of biologically important fluorine-containing phenylserines and related compounds,[14] prompted us to undertake the present investigation.

As it was shown earlier, for the particular case of benzaldehyde (**1a**) aldol reaction with methyl α-isocyanoacetate (**2a**), complex of bis(*c*-hexyl isocyanide)gold(I) tetrafluoroborate (**3**) with (*R*)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4a**) proved to be a superior catalyst for this condensation, providing formation of *trans*-oxazoline **5a** in 88% diastereomeric and 95% enantiomeric excess (de and ee respectively), (Scheme 2, Table 1, entry 1).[8b,c,h] Under the same reaction conditions *p*-fluoro-(**1b**) and *m*-fluorobenzaldehydes (**1c**) gave corresponding *trans*-oxazolines **5b** and **5c** (entries 2, 3) in the excellent chemical yields (97% for **5b** and 96% for **5c**), diastereo- (86%, 82%) and enantioselectivities (94%, 93%). At the lower temperature (0 °C) we have improved both diastereo- and enantioselectivity for *trans*-oxazolines **5b** and **5c** up to 88% de and over 95% ee (entries 4, 5). A little lower selectivity was observed for *o*-fluorobenzaldehyde (**1d**) reaction with **2a** (entries 6, 7). The absolute

Scheme 2

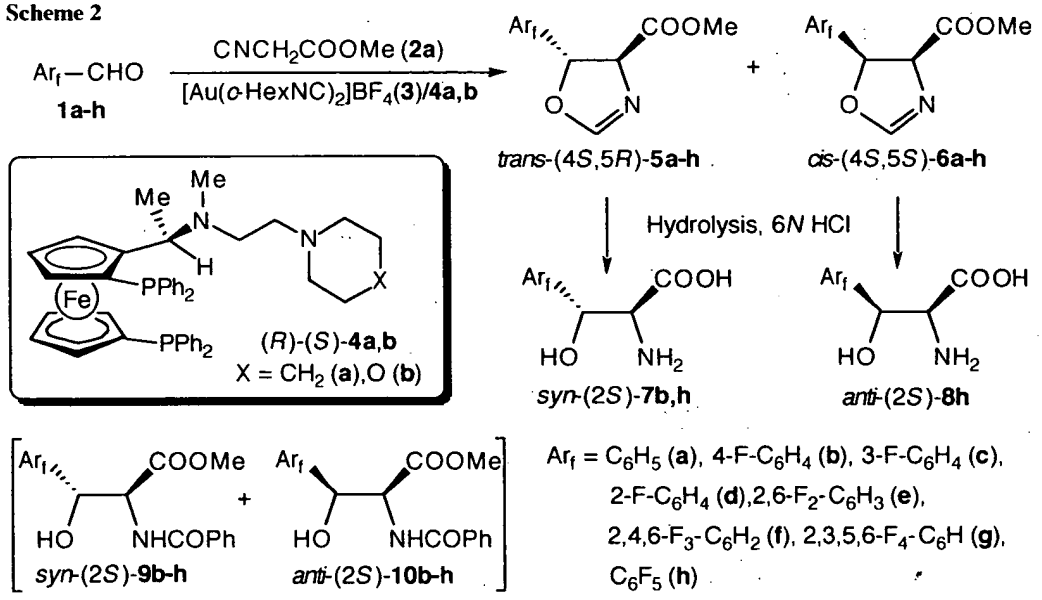


Table 1. Gold(I)-Catalyzed Asymmetric Aldol Reaction of Fluorobenzaldehydes **1b-h** with **2a**[a]

entry	Ar_f in aldehyde (**1**)	conditions ligand	temp(°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**5**/*cis*-**6**	% ee[d] *trans*-**5**	*cis*-**6**
1[e]	C_6H_5 (**a**)	**4a**	25	20-40	94	94 / 6	95	49[f]
2	4-F-C_6H_4 (**b**)	**4a**	25	10	97	93 / 7	94	20
3	3-F-C_6H_4 (**c**)	**4a**	23	10	96	91 / 9	93	23
4	4-F-C_6H_4 (**b**)	**4a**	0	100	96	94 / 6	96	19
5	3-F-C_6H_4 (**c**)	**4a**	0	100	97	94 / 6	95	20
6	2-F-C_6H_4 (**d**)	**4a**	23	10	96	84 / 14	84	38
7	2-F-C_6H_4 (**d**)	**4a**	1	45	99	89 / 11	90	40
8	2,6-F_2-C_6H_3 (**e**)	**4a**	0	79	98	75 / 25	86	78
9	2,4,6-F_3-C_6H_2 (**f**)	**4a**	0	100	96	67 / 33	73	82
10	2,3,5,6-F_4-C_6H (**g**)	**4a**	0	71	90	47 / 53	48	89
11	C_6F_5 (**h**)	**4a**	1	21	94	47 / 53	28	79
12	C_6F_5 (**h**)	**4a**	23	1	91	67 / 33	23	67
13[e]	C_6H_5 (**a**)	**4b**	25	20-40	93	95 / 5	95	12[g]
14	C_6F_5 (**h**)	**4b**[h]	0	100	96	37 / 63	36	86
15	2,3,5,6-F_4-C_6H (**g**)	**4b**[h]	0	70	93	38 / 62	33	90
16	4-F-C_6H_4 (**b**)	**4b**	0	70	92	94 / 6	94	25

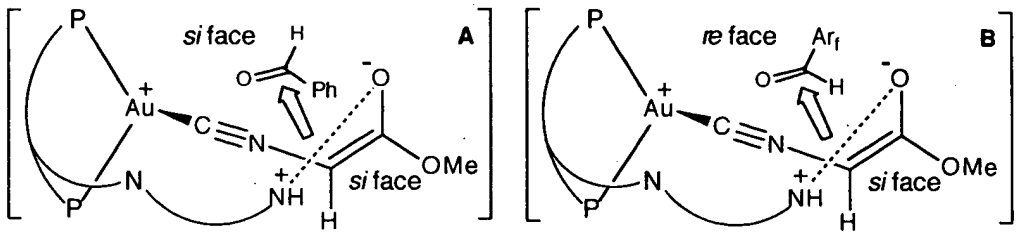
[a] The reactions were carried out in dichloromethane under argon atmosphere. The gold catalyst was prepared *in situ* from [Au(*c*-HexNC)$_2$]BF_4 **3** and corresponding chiral ligand **4a** or **4b**. Ratio of **1b-h**/**2a**/**3**/**4a,b** = 1/1.1/0.01/0.011 unless otherwise noted. [b] Isolated yield by bulb-to-bulb distillation. [c] Determined by ^{1}H NMR analysis. [d] Determined by chiral HPLC analysis of methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionates **9**,**10** with a chiral stationary phase column (SUMICHIRAL OA-2000 or 2000I), hexane/1,2-dichloroethane/ethanol = 100/20/1. The absolute configuration of all the *trans*-oxazolines **5** is assigned to be (4*S*,5*R*), and of *cis*-**6** to be (4*S*,5*S*) by similarity in the order of elution of derivatives **9**, **10** under the conditions of chiral HPLC analysis. See also text. [e] Previously published data, see text. [f] Absolute configuration is (4*R*,5*R*). [g] Absolute configuration is (4*S*,5*S*). [h] 2 Mol % of catalyst (**3**/**4b**) was used.

configuration of the *trans*-oxazoline **5b** was determined to be (4*S*,5*R*), the same as that of **5a**, by converting it into the known free *syn*-(2*S*)-β-(*p*-fluorophenyl)serine **7b** [(2*S*,3*R*)-**7b**].

The next experiments with di-, tri-, tetra- and pentafluorosubstituted benzaldehydes **1e-h**, which were done under the same reaction conditions at 0-1 °C using 1 mol % of the catalyst (**3**/**4a**), have revealed a surprising influence of the number of fluorine atoms in the phenyl ring of starting benzaldehyde on the stereochemical outcome of aldol reactions (entries 8-11 vs 2-7). Thus, the increase of fluorine substitution for hydrogen in the series of fluorobenzaldehydes **1e-h** was accompanied by gradual increase of the ratio of *cis*-oxazolines **6e-h** and their enantiomeric purity as well. On the other hand, the ee values of the corresponding *trans*-oxazolines **5e-h**, formed in the reactions of **1e-h** with **2a**, were gradually decreasing. The extremes of this trend, 57% of cis-diastereoselectivity, were observed in the tetrafluoro-**1g** and pentafluorobenzaldehyde (**1h**) reaction with isocyanoacetate **2a** (entries 10, 11). Enantiomeric purity of *cis*-oxazolines **6g,h** was shown to be 89 and 79% ee, respectively. At room temperature (entry 12), ratio of *trans*-oxazoline **5h** in the reaction of **1h** with **2a** was markedly increased, however ee of both *trans*- and *cis*-oxazolines **5h** and **6h** was low.

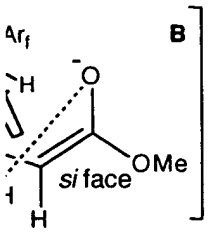
For determination of oxazolines **5h** and **6h** absolute configuration, they were separated and then, each of them was hydrolyzed to give corresponding β-(pentafluorophenyl)serines **7h** and **8h** of known configuration. Comparison of $[\alpha]_D$ values of amino acids **7h** and **8h** obtained with that reported in literature (see experimental) has revealed their *syn*-(2*S*) and *anti*-(2*S*) configuration respectively, and consequently (4*S*,5*R*) configuration for

Figure 1. Proposed Transition-States Models for the Gold-Catalyzed Aldol Reaction



trans-**5h** and (4*S*,5*S*) for *cis*-oxazoline **6h**. With these results in hands we suggested that chiral ferrocenylphosphine ligand **4b**, bearing a morpholino residue on the terminal position of the pendant side chain, which in contrary to **4a** provides (4*S*,5*S*) absolute configuration of corresponding *cis*-oxazoline in the reaction of **1a** with **2a** (entry 13), might increase stereoselectivity of polyfluorobenzaldehydes reactions with isocyanoacetate **2a**. Indeed, application of morpholino derived ligand **4b** in the complex with gold(I) **3** for catalysis of aldol reactions of aldehydes **1g** and **1h** with **2a** has improved both the ratio of *cis*-oxazolines **6g** (62%) and **6h** (63%) and their enantiomeric purity (90% and 86% ee, respectively), (entries 14, 15). Reaction of *p*-fluorobenzaldehyde (**1b**) with isocyanoacetate **2a**, catalyzed by the complex **3/4b**, gave a stereochemical outcome similar to that of benzaldehyde (**1a**) reaction (entries 13 vs 16).

As it follows from the results obtained, gold(I) **3**/chiral ferrocenylphosphine ligand **4a,b**-catalyzed aldol reactions of methyl α-isocyanoacetate (**2a**) with tetrafluoro- **1g** and pentafluorobenzaldehydes (**1h**), in sharp contrast to that of benzaldehyde (**1a**) or monofluorosubstituted benzaldehyde reactions **1b-d**, gave corresponding *cis*-oxazolines **6g,h** as the main reaction products with high % ee. The gradual inversion of the stereochemical result of aldol reactions under investigation, brought about by fluorine atoms, was totally unexpected. The reasons behind the phenomenon could be reasonably ascribed to the increasing electrophilicity (electron-deficiency) of a phenyl ring in the series from mono- to pentafluorosubstituted benzaldehydes **1b-h**. The working model for the transition-state of the stereoselective step of the gold(I)-catalyzed aldol reaction postulates the following features (Figure 1, transition-state **A**): a) the gold(I) cation is co-ordinated to the two phosphorus atoms of ferrocenylphosphine ligand, and the carbon of the isocyanoacetate ester; b) the enolate anion of the isocyanoacetate is formed by the abstraction of one of the active protons by the terminal dialkylamino group of the ligand pendant side chain. The chiral environment of the enolate formed determines electrophilic attack by the *si*-face of an aldehyde on the si-face of the enolate. This mode of interactions (transition-state **A**) provides *trans*-oxazoline formation. The stereochemistry of the products **5h**, **6h** suggests that favorable electrophilic attack of pentafluorobenzaldehyde (**1h**) occurs on the same enolate π-face while the carbonyl π-face selectivity is different than that of the benzaldehyde (**1a**) reaction. Sterically unfavorable transition-state **B**, which leads to the formation of *cis*-(4*S*,5*S*)-oxazoline **6h**, could be stabilized by π-p attractive interaction between the electron-deficient pentafluorophenyl ring and the negatively charged enolate anion. The assumption that the electron-deficient nature of the polyfluorophenyl ring is responsible for an enhanced *cis*-diastereoselectivity, observed in the reactions of fluorinated benzaldehydes with isocyanoacetate **2a**, is supported by the other examples of the gold(I)-catalyzed aldol condensations of **2a** with benzaldehydes bearing strongly electron-withdrawing substituents. Thus, for instance, reaction of *p*-nitrobenzaldehyde with **2a**, catalyzed by 1 mol % of **3/4b**, gave 83/17 (vs 95/5 for benzaldehyde) ratio of *trans*-(2*R*,3*S*)/*cis*-(2*S*,3*S*)-oxazolines with lowered ee (86% ee) of *trans*-isomer and quite high ee (75% ee) of *cis*-oxazoline,[8h] as compared with the corresponding values of benzaldehyde reaction with **2a** (Table 1, entry 13). There is also a very close analogy between our observations and the results reported by Ojima and Kwon on the unique stereodifferentiation disclosed for pentafluorophenyl-containing chiral iron acyl complex (PFCHIRAC).[15] They had proven that this very case of electron donor-acceptor type attractive interaction between the enolate oxygen and pentafluorophenyl moiety caused the opposite stereochemical outcome in the addition reactions of PFCHIRAC and fluorine-free CHIRAC.[16]



suggested that chiral
the pendant side chain,
oxazoline in the reaction
ehydes reactions with
plex with gold(I) **3** for
tio of *cis*-oxazolines **6g**
tries 14, 15). Reaction
, gave a stereochemical

nd **4a,b**-catalyzed aldol
dehydes (**1h**), in sharp
reactions **1b-d**, gave
gradual inversion of the
rine atoms, was totally
creasing electrophilicity
d benzaldehydes **1b-h**.
catalyzed aldol reaction
co-ordinated to the two
ate ester; b) the enolate
rotons by the terminal
olate formed determines
s mode of interactions
oducts **5h**, **6h** suggests
enolate π-face while the
Sterically unfavorable
d be stabilized by π-p
gatively charged enolate
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ies with isocyanoacetate
2a with benzaldehydes
-nitrobenzaldehyde with
ns-(2*R*,3*S*)/*cis*-(2*S*,3*S*)-
) of *cis*-oxazoline,[8h] as
try 13). There is also a
d Kwon on the unique
(PFCHIRAC).[15] They
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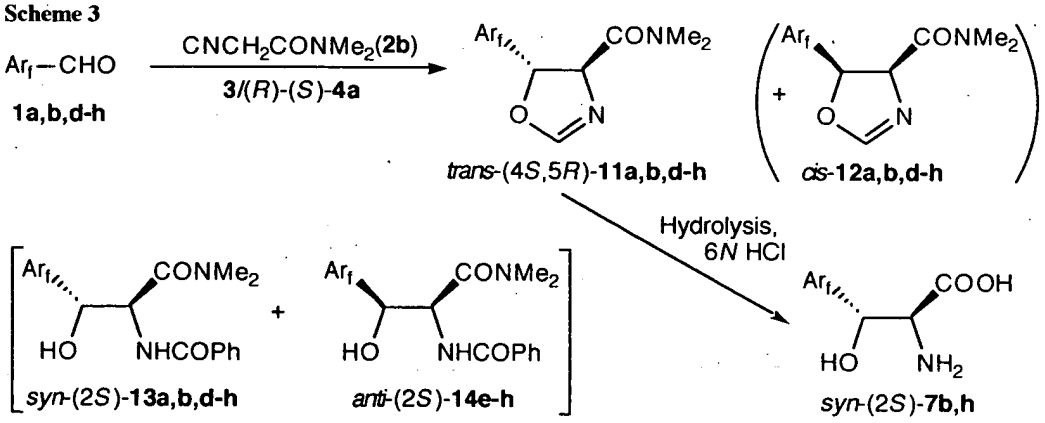
addition reactions of

Based on this reasoning, we envisioned that the application of *N*,*N*-dimethyl-α-isocyanoacetamide (**2b**) instead of methyl isocyanoacetate (**2a**), due to the both electronic and steric factors, might disturb transition-state **B** (Figure 1) and thus enhance the *trans*-diastereoselectivity of the polyfluorobenzaldehydes aldol reactions. Previously, *N*,*N*-dialkyl-α-isocyanoacetamides were used to increase both enantio- and *trans*-selectivity in the gold(I)-catalyzed aldol reactions of less sterically demanded primary alkyl aldehydes.[8l] Stereoselectivity of benzaldehyde (**1a**) reaction with **2b** (Scheme 3), catalyzed by 1 mol % of **3**/**4a**, was shown to be similar to that of **1a** condensation with isocyanoacetate **2a** (Table 1, entry 1 vs Table 2, entry 1).[8l] Firstly, we investigated reaction of isocyanoacetamide **2b** with pentafluorobenzaldehyde (**1h**) which was, in the light of the results discussed above, expected to display the most significant difference in the reactivity and selectivity from fluorine-free benzaldehyde (**1a**) (Scheme 3). In accordance with our expectation, the reaction of pentafluorobenzaldehyde (**1h**) with isocyanoacetamide **2b**, performed at 25 °C in the presence of 1 mol % of **3**/**4a**, gave a mixture of *trans*/*cis*-oxazolines **11h** and **12h** with remarkable domination of *trans*-**11h**, albeit formed with moderate ee (Table 1, entry 2). Lowering of the reaction temperature and application of 2 mol % of the catalyst (**3**/**4a**) allowed marked increase of enantioselectivity for *trans*-oxazoline **11h** formation, however, with a bit lower diastereoselectivity (entry 3). For determination of the absolute configuration of the amino acid moiety in the oxazoline **11h**, it was hydrolyzed to give known β-(pentafluorophenyl)serine **7h**. Comparison of $|\alpha|_D$ value of amino acid **7h** obtained with the literature value established its *syn*-(2*S*) absolute configuration and, consequently, the (4*S*,5*R*) absolute configuration of *trans*-oxazoline **11h**. Similar reactivity and stereochemical outcome were observed in the aldol reaction of 2,3,5,6-tetrafluorobenzaldehyde (**1g**) with isocyanoacetamide **2b** (entries 4, 5). Thus, the highest *trans*-selectivity (89%) with 77% ee of oxazoline **11g** was observed at 20 °C, whilst low temperature reaction gave *trans*-oxazoline **11g** with 84% of diastereoselectivity and 84% ee.

In the aldol reactions of trifluoro- and difluorobenzaldehydes **1f** and **1e** with isocyanoacetamide **2b** (entries 6 and 7, respectively), the desirable *trans*-oxazolines **11f** and **11e** were obtained with both higher diastereo and enantioselectivity (91% ee for **11f** and 93% ee for **11e**) than the corresponding *trans*-oxazolines **5f** and **5e** (Scheme 2, Table 1, entries 9, 8) in the reaction of **1f,e** with isocyanoacetate **2a**. Finally, the aldol reactions of isocyanoacetamide **2b** with monofluorosubstituted benzaldehydes **1b,d** gave *trans*-oxazolines **11b** and **11d** with the expected high diastereo- and enantioselectivities (entries 9 and 8, respectively). However, the use of isocyanoacetamide **2b** for the synthesis of corresponding *syn*-(2*S*)-β-(monofluorophenyl)serines **7**, through oxazolines **11b,d**, seemed to have no advantages over the application of isocyanoacetate **2a**, which provided a better stereochemical outcome of corresponding oxazolines **5b,d**.

Scheme 3



Ar$_f$ = C_6H_5 (**a**), 4-F-C_6H_4 (**b**), 2-F-C_6H_4 (**d**), 2,6-F_2-C_6H_3 (**e**), 2,4,6-F_3-C_6H_2 (**f**), 2,3,5,6-F_4-C_6H (**g**), C_6F_5 (**h**)

Table 2. Gold(I)-Catalyzed Asymmetric Aldol Reactions of Fluorobenzaldehydes **1b,d-h** with **2b**[a]

entry	Ar[1] in aldehyde **1**	conditions temp(°C)	time (h)	yield[b] (%)	ratio[c] *trans*-**11**/*cis*-**12**	% ee[d] *trans*-**11**	*cis*-**12**
1[e]	C_6H_5 (**a**)	25	25	74[f]	94/6	94	-
2	C_6F_5 (**h**)	25	24[g]	87	81/19	68	24
3	C_6F_5 (**h**)	15[h]	48	82	77/23	80	20
4	2,3,5,6-F_4-C_6H (**g**)	20	20	88	89/11	77	28
5	2,3,5,6-F_4-C_6H (**g**)	15[h]	50	78	84/16	84	26
6	2,4,6-F_3-C_6H_2 (**f**)	10	48	83	85/15	91	48
7	2,6-F_2-C_6H_3 (**e**)	20	25	84	77/23	93	64
8	2-F-C_6H_4 (**d**)	22	25	87	83/13	93	-
9	4-F-C_6H_4 (**b**)	20	24	89	92/8	94	-

[a] The reactions were carried out in dichloromethane under argon atmosphere. The gold catalyst was prepared *in situ* from [Au(*c*-HexNC)$_2$]BF_4 (**3**) and chiral ligand **4a**. Ratio of **1**/**2b**/**3**/**4a** = 1.3/1/0.02/0.022 unless otherwise noted. [b] Isolated yield after passing reaction mixture through a short silica gel column (3×1.5 cm) using ethyl acetate as an eluent. [c] Determined by ^{1}H NMR analysis. [d] Determined by HPLC analysis of *NN*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionamides **13, 14** with a chiral stationary phase column (SUMICHIRAL OA-2000, 2000I, 4500, or 4900), hexane/1,2-dichloroethane/ethanol = 50/15/1, 100/20/1, or 250/20/1. The absolute configuration of **11h** was determined to be (4*S*,5*R*) (see text). All other *trans*-oxazolines **11b,d-g** are assumed to have the same (4*S*,5*R*) configuration by similarity in the order of elution under the condition of chiral HPLC analysis. The absolute configuration of the *cis*-oxazolines **12** was not determined. [e] Previously reported data, see ref. 8d. [f] Yield of *trans*-oxazoline **6h**, see ref. 8d. [g] One mol % of the catalyst was used. [h] Reaction was started at 0 °C and then reaction temperature was allowed to rise to 15 °C.

CONCLUSIONS

The present results have revealed that the stereochemical outcome of the gold(I)-catalyzed asymmetric aldol reactions studied dramatically depends on the nature of both fluorobenzaldehyde and isocyanoacetic acid derivative being used. The result of methyl α-isocyanoacetate (**2a**) reactions with fluorinated benzaldehydes was shown to be controlled by the number of fluorine atoms in the aryl moiety of fluorobenzaldehyde used. Thus, aldol condensations of **2a** with monofluorobenzaldehydes furnished *trans*-oxazolines with more than 90% of *trans*-diastereoselectivity and % ee, while in the case of the reactions with polyfluorobenzaldehydes corresponding *cis*-oxazolines were formed as dominant isomers with high ee (up to 90% ee). In marked contrast to this, reactions of *N*,*N*-dimethyl-α-isocyanoacetamide (**2b**) with fluorobenzaldehydes provided preferential formation and high % ee of *trans*-oxazolines regardless of the fluorosubstituted benzaldehyde used. It follows that both *syn*-and *anti*-β-(polyfluorophenyl)serines can be prepared selectively in high enantiomeric purity *via* gold(I)-catalyzed asymmetric aldol reaction by use of amide **2b** and ester **2a**, respectively. Lastly, the reactive π-face of the enolate formed from amide **2b** or ester **2a**, being controlled by chiral ferrocenylphosphine ligand, was shown to be the same for the reactions of hydrocarbon and fluorocarbon aryl aldehydes.

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EXPERIMENTAL PART

General. ^{1}H NMR spectra were recorded with a JEOL (300 MHz) spectrometer. Chemical shifts are reported in δ ppm relative to TMS [$(CH_3)_4Si$] in $CDCl_3$. Optical rotations were measured on a Perkin-Elmer 243 polarimeter. Preparative medium-pressure liquid chromatography (MPLC) was performed with a silica gel 60 pre-packed Lobar (Merck) column. Chiral HPLC analyses of methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionates **9**,**10** and *N*,*N*-dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(fluorophenyl)propionamides **13**, **14** were performed on a Jasco HPLC system using chiral stationary phase columns SUMICHIRAL OA-2000, 2000I, 4500, or 4900, hexane/1,2-dichloroethane/ethanol = 50/15/1, 100/20/1, or 250/20/1 for determination of enantiomeric composition of **13**, **14**, and SUMICHIRAL OA-2000 or 2000I (hexane/1,2-dichloroethane/ethanol = 100/20/1) for **9**,**10**. Fluoro-aldehydes **1b-h** and methyl α-isocyanoacetate (**2a**) are commercially available. *N*,*N*-Dimethyl-α-isocyanoacetamide (**2b**) was prepared by the reaction of isocyanoacetate **2a** with dry dimethylamine in methanol,[17] and prior to use was crystallized from hexane/benzene to give colorless needle shape crystals. Bis(*c*-hexyl isocyanide)gold(I) tetrafluoroborate (**3**) was prepared as described in the literature.[18] Chiral ligands (*R*)-*N*-methyl-*N*-[2-(piperidino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4a**), (*R*)-*N*-methyl-*N*-[2-(morpholino)ethyl]-1-[(*S*)-1',2-bis(diphenylphosphino)ferrocenyl]ethylamine (**4b**) were prepared by the reaction of (*R*)-1-[(*S*)-1'2-bis(diphenylphosphino)ferrocenyl]ethyl acetate with an appropriate amine according to the reported procedure.[8h,11]

Aldol Reactions of Isocyanoacetic Acid Derivatives 2a,b with Fluoro-Benzaldehydes 1b-h. General Procedure. To a stirred solution of gold(I) tetrafluoroborate **3** (0.010 mmol), chiral ferrocenylphosphine ligand **4a,b** (0.010-0.011 mmol) and methyl α-isocyanoacetate (**2a**) or *N*,*N*-dimethyl-α-isocyanoacetamide (**2b**) (1.0 mmol) in 2 mL of freshly distilled dichloromethane, appropriate fluorobenzaldehyde **1b-h** (1.0-1.1 mmol) was added under nitrogen. The resulted mixture was stirred until all of the **2a** or **2b** had been consumed (monitored by GC and TLC). Reaction temperature and time are indicated in the Tables 1 and 2. After completion of the reaction solvent was evaporated under reduced pressure and the residual material was either bulb-to-bulb distilled or passed through a short silica gel column (3×1.5 cm, ethyl acetate as an eluent) to provide the oxazolines **5,6b-h**, starting from **2a**, and **11,12b,d-h**, starting from **2b**, as a colorless sticky oil. Racemic syntheses of corresponding oxazolines were accomplished in the same manner with the difference that $CuCl/NEt_3$ (0.1 mmol) was used instead of **3**/**4**. The ratio of *trans*/*cis* was determined by ^{1}H NMR spectra of the mixtures **5,6b-h** and **11,12b,d-h** obtained. Owing to an effect of aromatic ring, the methyl protons of methoxy or dimethylamino group in *cis*-oxazolines **6b-h** and **12b,d-h** respectively, shifted up-field in comparison with those of the *trans*-oxazolines **5b-h**, **11b,d-h**. Diastereomeric ratio (*trans*/*cis*) are given in the Tables 1 and 2. ^{1}H NMR spectra and micro-analytical data for oxazolines **5,6b-h** and **11,12b,d-h** are listed below.

4-(Methoxycarbonyl)-5-(4-fluorophenyl)-2-oxazolines **5,6b**: *trans*-**5b**, 3.84 (s, 3 H), 4.59 (dd, *J* = 7.9 Hz, 2.3 Hz, 1 H), 5.67 (d, *J* = 7.9 Hz, 1 H), 7.00-7.26 (m, 3 H), 7.28-7.33 (m, 2 H); *cis*-**6b**, 3.25 (s, 3 H), 5.08 (dd, *J* = 11.2 Hz, 2.1 Hz, 1 H), 5.73 (d, *J* = 11.2 Hz, 1 H), 7.05-7.24 (m, 3 H), 7.28-7.30 (m, 2 H). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.29; H, 4.31; N, 6.44.

4-(Methoxycarbonyl)-5-(3-fluorophenyl)-2-oxazolines **5,6c**: *trans*-**5c**, 3.85 (s, 3 H), 4.60 (dd, *J* = 7.9 Hz, 2.2 Hz, 1 H), 5.69 (d, *J* = 7.9 Hz, 1 H), 6.95-7.41 (m, 5 H); *cis*-**6c**, 3.27 (s, 3 H), 5.10 (dd, *J* = 11.2 Hz, 2.0 Hz, 1 H), 5.73 (d, *J* = 11.2 Hz, 1 H), 7.05-7.34 (m, 5 H). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.35; H, 4.66; N, 6.21.

4-(Methoxycarbonyl)-5-(2-fluorophenyl)-2-oxazolines **5,6d**: *trans*-**5d**, 3.84 (s, 3 H), 4.66 (dd, *J* = 7.6 Hz, 1.3 Hz, 1 H), 5.92 (d, *J* = 7.6 Hz, 1 H), 7.10-7.37 (m, 5 H); *cis*-**6d**, 3.25 (s, 3 H), 5.13 (dd, *J* = 10.9 Hz, 1.6 Hz, 1 H), 6.00 (d, *J* = 10.9 Hz, 1 H), 7.10-7.37 (m, 5 H). Anal. Calcd for $C_{11}H_{10}FNO_3$: C, 59.19; H, 4.52; N, 6.27. Found: C, 59.22; H, 4.49; N, 6.38.

4-(Methoxycarbonyl)-5-(2,6-difluorophenyl)-2-oxazolines **5,6e**: *trans*-**5e**, 3.82 (s, 3 H), 4.80 (dd, *J* = 8.5 Hz, 2.0 Hz, 1 H), 6.02 (d, *J* = 8.5 Hz, 1 H), 6.84-6.97 (m, 2 H), 7.01 (d, *J* = 2.0 Hz, 1 H), 7.23-7.36 (m, 1 H); *cis*-**6e**, 3.40 (s, 3 H), 5.18 (dd, *J* = 11.9 Hz, 2.3 Hz, 1 H), 6.10 (d, *J* = 11.9 Hz, 1 H), 6.81-6.93 (m, 2 H), 7.09 (d, *J* = 2.3 Hz, 1 H), 7.21-7.32 (m, 1 H). Anal. Calcd for $C_{11}H_9F_2NO_3$: C, 54.77; H, 3.76; N, 5.81. Found: C, 55.01; H, 3.78; N, 5.94.

4-(Methoxycarbonyl)-5-(2,4,6-trifluorophenyl)-2-oxazolines **5,6f**: *trans*-**5f**, 3.83 (s, 3 H), 4.77 (dd, *J* = 8.3 Hz, 2.3 Hz, 1 H), 5.97 (d, *J* = 8.3 Hz, 1 H), 6.64-6.76 (m, 2 H), 6.99 (d, *J* = 2.3 Hz, 1 H); *cis*-**6f**, 3.48 (s, 3 H), 5.17 (dd, *J* = 11.7 Hz, 2.3 Hz, 1 H), 6.06 (d, *J* = 11.7 Hz, 1 H), 6.61-6.73 (m, 2 H), 7.09 (d, *J* = 2.3 Hz, 1 H). Anal. Calcd for $C_{11}H_8F_3NO_3$: C, 50.97; H, 3.11; N, 5.40. Found: C, 51.12; H, 3.21; N, 5.51.

4-(Methoxycarbonyl)-5-(2,3,5,6-tetrafluorophenyl)-2-oxazolines **5,6g**: *trans*-**5g**, 3.84 (s, 3 H), 4.81 (dd, J = 8.3 Hz, 2.3 Hz, 1 H), 6.03 (d, J = 8.3 Hz, 1 H), 7.01 (d, J = 2.3 Hz, ,1 H), 7.1 (m, 1 H); *cis*-**6g**, 3.53 (s, 3 H), 5.24 (dd, J = 11.5 Hz, 2.3 Hz, 1 H), 6.10 (d, J = 11.5 Hz, 1 H), 7.1 (d, J = 2.3 Hz, 1 H), 7.2 (m, 1 H). Anal. Calcd for $C_{11}H_7F_4NO_3$: C, 47.66; H, 2.55; N, 5.05. Found: C, 47.74; H, 2.57; N, 5.19.

4-(Methoxycarbonyl)-5-pentafluorophenyl-2-oxazolines **5,6h**: *trans*-**5h**, 3.85 (s, 3 H), 4.79 (dd, J = 8.3 Hz, 2.3 Hz, 1 H), 5.99 (d, J = 8.3 Hz, 1 H), 7.00 (d, J = 2.3 Hz, 1 H); *cis*-**6h**, 3.57 (s, 3 H), 5.21 (dd, J = 11.6 Hz, 2.3 Hz, 1 H), 6.06 (d, J = 11.6 Hz, 1 H), 7.09 (d, J = 2.3 Hz, 1 H). Anal. Calcd for $C_{11}H_6F_5NO_3$: C, 44.76; H, 2.05; N, 4.75; F, 32.19. Found: C, 44.91; H, 2.01; N, 4.55; F, 32.23.

5-(4-Fluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12b**: *trans*-**11b**, 2.90 (s, 3 H), 3.11 (s, 3 H), 4.53 (dd, J = 7.9 Hz, 2.1 Hz, 1 H), 6.06 (d, J = 7.9 Hz, 1 H), 6.88 (d, J = 2.1 Hz, ,1 H), 6.92-7.21 (m, 4 H); *cis*-**12b**, 2.63 (s, 3 H), 2.73 (s, 3 H), 5.20 (dd, J = 10.9 Hz, 2.0 Hz, 1 H), 5.49 (d, J = 10.9 Hz, 1 H), 6.91-7.20 (m, 5 H). Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.54; N, 11.86. Found: C, 60.93; H, 5.55; N, 11.93.

5-(2-Fluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12d**: *trans*-**11d**, 3.00 (s, 3 H), 3.17 (s, 3 H), 4.71 (dd, J = 7.8 Hz, 2.1 Hz, 1 H), 6.22 (d, J = 7.8 Hz, 1 H), 6.93 (d, J = 2.1 Hz, 1 H), 7.05-7.30 (m, 4 H); *cis*-**12d**, 2.62 (s, 3 H), 2.88 (s, 3 H), 5.41 (dd, J = 10.2 Hz, 2.1 Hz, 1 H), 5.93 (d, J = 10.2 Hz, 1 H), 7.11-7.37 (m, 5 H). Anal. Calcd for $C_{12}H_{13}FN_2O_2$: C, 61.01; H, 5.54; N, 11.86. Found: C, 61.13; H, 5.62; N, 11.76.

5-(2,6-Difluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12e**: *trans*-**11e**, 2.94 (s, 3 H), 3.18 (s, 3 H), 4.83 (dd, J = 7.6 Hz, 2.3 Hz, 1 H), 6.53 (d, J = 7.6 Hz, 1 H), 6.85 (d, J = 2.3 Hz, 1 H), 7.44-7.58 (m, 3 H); *cis*-**12e**, 2.75 (s, 3 H), 2.91 (s, 3 H), 5.33 (dd, J = 11.3 Hz, 2.1 Hz, 1 H), 6.03 (d, J = 11.3 Hz, 1 H), 7.06 (d, J = 2.1 Hz, 1 H), 7.15-7.28 (m, 3 H). Anal. Calcd for $C_{12}H_{12}F_2N_2O_2$: C, 56.69; H, 4.76; N, 11.02. Found: C, 56.74; H, 4.89; N, 11.23.

5-(2,4,6-Trifluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12f**: *trans*-**11f**, 2.99 (s, 3 H), 3.24 (s, 3 H), 4.84 (dd, J = 7.6 Hz, 2.0 Hz, 1 H), 6.54 (d, J = 7.6 Hz, 1 H), 6.88 (d, J = 2.0 Hz, 1 H), 6.60-6.75 (m, 2 H); *cis*-**12f**, 2.68 (s, 3 H), 3.15 (s, 3 H), 5.36 (dd, J = 11.2 Hz, 2.1 Hz, 1 H), 6.03 (d, J = 11.2 Hz, 1 H), 6.63-6.76 (m, 2 H), 7.10 (d, J = 2.1 Hz, 1 H). Anal. Calcd for $C_{12}H_{11}F_3N_2O_2$: C, 52.94; H, 4.07; N, 10.29. Found: C, 53.04; H, 4.13; N, 10.31.

5-(2,3,5,6-Tetrafluorophenyl)-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12g**: *trans*-**11g**, 3.01 (s, 3 H), 3.26 (s, 3 H), 4.89 (dd, J = 7.8 Hz, 2.1 Hz, 1 H), 6.62 (d, J = 7.8 Hz, 1 H), 6.88 (d, J = 2.1 Hz, 1 H), 7.02-7.19 (m, 1 H); *cis*-**12g**, 2.75 (s, 3 H), 3.11 (s, 3 H), 5.42 (dd, J = 11.1 Hz, 2.1 Hz, 1 H), 6.05 (d, J = 11.1 Hz, 1 H), 7.01 (d, J = 2.1 Hz, 1 H), 7.00-7.15 (m, 1 H). Anal. Calcd for $C_{12}H_{10}F_4N_2O_2$: C, 49.66; H, 3.47; N, 9.65. Found: C, 49.81; H, 3.56; N, 9.71.

5-Pentafluorophenyl-2-oxazoline-4-(*N*,*N*-dimethyl)carboxamides **11,12h**: *trans*-**11h**, 3.02 (s, 3 H), 3.26 (s, 3 H), 4.86 (dd, J = 7.6 Hz, 2.1 Hz, 1 H), 6.59 (d, J = 7.6 Hz, 1 H), 6.89 (d, J = 2.1 Hz, 1 H); *cis*-**12h**, 2.77 (s, 3 H), 3.13 (s, 3 H), 5.43 (dd, J = 11.2 Hz, 2.1 Hz, 1 H), 5.98 (d, J = 11.2 Hz, 1 H), 7.08 (d, J = 2.1 Hz, 1 H). Anal. Calcd for $C_{12}H_9F_5N_2O_2$: C, 46.76; H, 2.94; N, 9.09. Found: C, 46.92; H, 2.83; N, 9.17.

Transformation of Oxazolines 5,6b-h and 11,12b,d-h into the *N*-Benzoyl Derivatives 9,10b-h and 13b,d-h, 14e-h. General Procedure. To a stirred solution of oxazolines **5,6** or **11,12** (1.0 mmol) 10 mL of methanol 1.5 mL of conc. HCl was added. The resulted mixture was stirred at 50 °C for 2 hrs.. and evaporated under reduced pressure to dryness. The residual material was dissolved or suspended in 5 mL of dichloromethane and treated with triethylamine (3.0 mmol) and then with benzoyl chloride (1.1 mmol). The resulted mixture was stirred at r.t. for 2 hrs. and evaporated under reduced pressure. Desired *N*-benzoyl derivatives were isolated with preparative TLC plates (hexane/ethyl acetate 2-1/1) and after confirmation of their structure by ^{1}H NMR spectra, they were subjected to chiral HPLC analysis. Racemic *N*-benzoyl derivatives, for being used as standards for HPLC analysis of optically active **9,10,13,14**, were prepared according to the same procedure starting from corresponding racemic oxazolines. ^{1}H NMR spectra of *N*-benzoyl derivatives **9,10b-h** and **13b,d-h**, **14e-h** are listed below.

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(4-fluorophenyl)propionates **9,10b**: *syn*-**9b**, 3.68 (s, 3 H), 4.98 (dd, J = 8.9 Hz, 3.3 Hz, 1 H), 5.31 (d, J = 3.3 Hz, 1 H), 7.16 (br d, J = 8.9 Hz, 1 H), 6.95-7.69 (m, 9 H); *anti*-**10b**, 3.67 (s, 3 H), 5.09 (dd, J = 7.6 Hz, 3.3 Hz, 1 H), 5.26 (d, J = 3.3 Hz, 1 H), 7.07 (br d, J = 7.6 Hz, 1 H), 7.00-7.68 (m, 9 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(3-fluorophenyl)propionates **9,10c**: *syn*-**9c**, 3.72 (s, 3 H), 5.03 (dd, J = 8.9 Hz, 3.0 Hz, 1 H), 5.36 (d, J = 3.0 Hz, 1 H), 6.93-7.61 (m, 9 H); *anti*-**10c**, 3.71 (s, 3 H), 5.14 (dd, J = 7.3 Hz, 3.3 Hz, 1 H), 5.31 (d, J = 3.3 Hz, 1 H), 6.90-7.72 (m, 9 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2-fluorophenyl)propionates **9,10d**: *syn*-**9d**, 3.80 (s, 3 H), 5.17 (dd, J = 8.6 Hz, 3.0 Hz, 1 H), 5.69 (d, J = 3.0 Hz, 1 H), 6.91 (br d, J = 8.6 Hz, 1 H), 7.00-7.68 (m, 9 H); *anti*-**10d**, 3.82 (s, 3 H), 5.20 (dd, J = 6.6 Hz, 3.0 Hz, 1 H), 5.66 (d, J = 3.0 Hz, 1 H), 7.05-7.71 (m, 10 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,6-difluorophenyl)propionates **9**,**10e**: *syn*-**9e**, 3.75 (s, 3 H), 5.17 (dd, *J* = 8.3 Hz, 4.6 Hz, 1 H), 5.64 (d, *J* = 4.6 Hz, 1 H), 6.85 (m, 2 H), 7.23 (m, 2 H), 7.50 (m, 3 H), 7.78 (m, 2 H); *anti*-**10e**, 3.80 (s, 3 H), 5.27 (dd, *J* = 7.3 Hz, 4.7 Hz, 1 H), 5.58 (m, 1 H), 6.90 (m, 2 H), 7.01 (m, 1 H), 7.25 (m, 1 H), 7.53 (m, 3 H), 7.72 (m, 2 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,4,6-trifluorophenyl)propionates **9**,**10f**: *syn*-**9f**, 3.77 (s, 3 H), 5.17 (m, 1 H), 5.60 (m, 1 H), 6.61 (m, 2 H), 7.00 (m, 1 H), 7.23 (m, 3 H), 7.75 (m, 2 H); *anti*-**10f**, 3.82 (s, 3 H), 5.25 (m, 1 H), 5.55 (m, 1 H), 6.62 (m, 2 H), 7.21 (m, 1 H), 7.22 (m, 3 H), 7.77 (m, 2 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(2,3,5,6-tetrafluorophenyl)propionates **9**,**10g**: *syn*-**9g**, 3.84 (s, 3 H), 5.21 (m, 1 H), 5.63 (m, 1 H), 7.01 (m, 1 H), 7.17 (m, 1 H), 7.25 (m, 3 H), 7.75 (m, 2 H). *anti*-**10g**, 3.80 (s, 3 H), 5.31 (m, 1 H), 5.62 (m, 1 H), 7.01 (m, 1 H), 7.38 (m, 1 H), 7.22 (m, 3 H), 7.76 (m, 2 H).

Methyl 2-(*N*-benzoylamino)-3-hydroxy-3-(pentafluorophenyl)propionates **9**,**10h**: *syn*-**9h**, 3.80 (s, 3 H), 5.18 (dd, *J* = 8.2 Hz, 4.9 Hz, 1 H), 5.65 (d, *J* = 4.9 Hz, 1 H), 7.23 (br d, *J* = 8.2 Hz, 1 H), 7.48 (m, 3 H), 7.81 (m, 2 H); *anti*-**10h**, 3.85 (s, 3 H), 5.29 (dd, *J* = 6.6 Hz, 4.3 Hz, 1 H), 5.63 (d, *J* = 4.3 Hz, 1 H), 7.07 (br d, *J* = 6.6 Hz, 1 H), 7.50 (m, 3 H), 7.80 (m, 2 H).

syn-*N*,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(4-fluorophenyl)propionamide **13b**, 2.86 (s, 3 H), 2.90 (s, 3 H), 4.75 (d, *J* = 2.0 Hz, 1 H), 5.04 (dd, *J* = 4.3 Hz, 2.0 Hz, 1 H), 5.18 (dd, *J* = 8.7 Hz, 4.3 Hz, 1 H), 6.90-6.96 (m, 2 H), 7.09 (d, *J* = 8.7 Hz, 1 H) 7.31-7.44 (m, 5 H), 7.63-7.67 (m, 2 H).

syn-*N*,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2-fluorophenyl)propionamides **13d**, 2.95 (s, 3 H), 3.16 (s, 3 H), 4.75 (d, *J* = 1.6 Hz, 1 H), 5.33 (dd, *J* = 8.9 Hz, 2.0 Hz, 1 H), 5.37 (m, 1 H), 6.95-7.07 (m, 3 H), 7.12-7.21 (m, 1 H), 7.28-7.52 (m, 4 H), 7.55-7.63 (m, 2 H).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,6-difluorophenyl)propionamides **13**,**14e**:*syn*-**13e**, 2.96 (s, 3 H), 3.18 (s, 3 H), 4.60 (m, 1 H), 5.43 (dd, *J* = 7.6 Hz, 6.9 Hz, 1 H), 5.70 (dd, *J* = 8.3 Hz, 6.9 Hz, 1 H), 6.77-6.88 (m, 2 H), 7.14-7.48 (m, 5 H), 7.62-7.71 (m, 2H); *anti*-**14e**, 2.91 (s, 3 H), 3.09 (s, 3 H), 4.22 (br.s, 1 H), 5.50 (m, 2 H), 6.80 (m, 2 H), 7.05-7.21 (m, 1 H), 7.31-7.44 (m, 4 H), 7.71-7.74 (m, 2H).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,4,6-trifluorophenyl)propionamides **13**,**14f**: *syn*-**13f**, 2.99 (s, 3 H), 3.21 (s, 3 H), 4.57 (d, *J* = 7.4 Hz, 1 H), 5.36 (dd, *J* = 7.4 Hz, 6.3 Hz, 1 H), 5.66 (dd, *J* = 7.9 Hz, 6.3 Hz, 1 H), 6.59 (t, *J* = 8.7 Hz, 2 H), 7.20 (d, *J* = 7.9 Hz, 1 H), 7.36-7.52 (m, 3 H), 7.67-7.70 (m, 2H); *anti*-**14f**, 2.95 (s, 3 H), 3.13 (s, 3 H), 4.41 (d, *J* = 5.0 Hz, 1 H), 5.42-5.46 (m, 2 H), 6.62 (t, *J* = 8.6 Hz, 2 H), 7.25-7.50 (m, 4 H), 7.76-7.79 (m, 2H).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(2,3,5,6-tetrafluorophenyl)propionamides **13**,**14g**:*syn*-**13g**, 2.95 (s, 3 H), 3.20 (s, 3 H), 4.96 (d, *J* = 7.6 Hz, 1 H), 5.40 (dd, *J* = 7.6 Hz, 5.7 Hz, 1 H), 5.62 (dd, *J* = 7.3 Hz, 5.7 Hz, 1 H), 6.91 (tt, *J* = 9.6 Hz, 7.6 Hz, 1 H), 7.19 (d, *J* = 7.3 Hz, 1 H), 7.33-7.45 (m, 3 H), 7.63-7.66 (m, 2H); *anti*-**14g**, 2.92 (s, 3 H), 3.12 (s, 3 H), 4.68 (br.s, 1 H), 5.40 (m, 1 H), 5.51 (dd, *J* = 5.3 Hz, 3.6 Hz, 1 H), 6.95 (tt, *J* = 9.6 Hz, 7.6 Hz, 1 H), 7.31-7.47 (m, 4 H), 7.68-7.72 (m, 2H).

N,*N*-Dimethyl-2-(*N*-benzoylamino)-3-hydroxy-3-(pentafluorophenyl)propionamides **13**,**14h**: *syn*-**13h**, 3.04 (s, 3 H), 3.28 (s, 3 H), 5.09 (d, *J* = 7.6 Hz, 1 H), 5.44 (dd, *J* = 7.6 Hz, 5.3 Hz, 1 H), 5.68 (dd, *J* = 7.3 Hz, 5.3 Hz, 1 H), 7.27 (d, *J* = 7.3 Hz, 1 H), 7.41-7.50 (m, 3 H), 7.71-7.75 (m, 2H). *anti*-**14h**, 3.03 (s, 3 H), 3.20 (s, 3 H), 4.61 (d, *J* = 4.4 Hz, 1 H), 5.43 (dd, *J* = 8.7 Hz, 3.3 Hz, 1 H), 5.57 (dd, *J* = 4.4 Hz, 3.3 Hz, 1 H), 7.33 (d, *J* = 8.7 Hz, 1 H), 7.44-7.56 (m, 3 H), 7.76-7.79 (m, 2H).

Preparative Synthesis of *syn*-(2*S*)-3-(4-Fluorophenyl)serine 7b, *syn*-(2*S*)-3-(Pentafluorophenyl)serine 7h, and *anti*-(2*S*)-3-(Pentafluorophenyl)serine 8h. General Procedure. Synthesis of oxazolines **5b**, **6h**, and **11b**,**h** was accomplished according to the general procedure given above. Yields of **5b**, **6h**, and **11b**,**h**, quantities of starting compounds, and reaction conditions are listed below. *trans*-(4*S*,5*R*)-Oxazoline **5b**: 395.96 mg (88.7%), starting from 273.05 mg (2.2 mmol) of *p*-fluorobenzaldehyde (**1b**), 198.18 mg (2 mmol) of isocyanoacetate **2a**, 9.76 mg (0.02 mmol) of **3** and 15.9 mg (0.022 mmol) of ferrocenylphosphine ligand **4a**, stirring in 4 mL of dichloromethane at 0 °C for 100 hrs, isolated by preparative MPLC; *cis*-(4*S*,5*S*)-**6h**: 335.3 mg (56.8%), [165.88 mg (28.1%) of **5h**], from 431.35 mg (2.2 mmol) of pentafluorobenzaldehyde (**1h**), 198 mg (2 mmol) of isocyanoacetate **1a**, 19.5 mg (0.04 mmol) of **3** and 31.9 mg (0.044 mmol) of ligand **4b**, stirring in 4 mL of dichloromethane at 0 °C for 100 hrs., isolated by preparative MPLC; *trans*-(4*S*,5*R*)-**11b**: 366.2 mg (77.5%), starting from 322.69 mg (2.6 mmol) of *p*-fluorobenzaldehyde (**1b**), 224.26 mg (2 mmol) of isocyanoacetamide **2b**, 19.5 mg (0.04 mmol) of **3** and 31.8 mg (0.044 mmol) of ferrocenylphosphine ligand **4a**, stirring in 4 mL of dichloromethane at 20 °C for 24 hrs., isolated by preparative TLC; *trans*-(4*S*,5*R*)-**11h**: 380.3 mg (61.7%), from 509.8 mg (2.6 mmol) of pentafluorobenzaldehyde (**1h**), 224.26 mg (2 mmol) of isocyanoacetamide **2b**, 19.5 mg (0.04 mmol) of **3** and 31.8 mg (0.044 mmol) of ligand **4a**, were mixed in 4 mL of dichloromethane at 0 °C and then stirred at 15 °C for 48 hrs., isolated by preparative TLC. Each of the oxazolines **5b**, **6h**, **11b**,**h** was dissolved in 20 mL MeOH, treated with 3 mL conc. HCl, and stirred at 50 °C for 2 hrs.. and then solution was evaporated under reduced pressure to dryness. The residual material was dissolved in 10 mL 6 *N* HCl and heated at 90-100 °C for 24 hrs.., for **7b** and **8h** from **5b**, **6h**,

respectively, and at 100 °C for 43 hrs.. (sealed tube), for **7b,h** from **11b,h**, and evaporated to dryness. The residual material was dissolved in methanol (15 mL) and treated with propylene oxide. Precipitated free amino acid was filtered off, washed with MeOH and dried in vacuum. Yields and $[\alpha]_D$ of amino acids **7b,h**, **8h** obtained were as follows: (2*S*,3*R*)-**7b**, 307 mg [87% from **5b**, and 71% (220 mg) from **11b**], $[\alpha]_D^{25}$ -20.0 (*c* 1, H_2O), lit.[5j] for (2*R*,3*S*)-enantiomer: $[\alpha]_D^{25}$ +20.5; (2*S*,3*S*)-**8h**, 258.7 mg (84% from **6h**), $[\alpha]_D^{25}$ +35.8 (*c* 1, 6 *N* HCl), lit.[5j] $[\alpha]_D^{25}$ +37.4; (2*S*,3*R*)-**7h**, 230.9 mg (69% from **11h**), $[\alpha]_D^{25}$ +12.1 (*c* 0.5, 6 *N* HCl), lit.[5j] $[\alpha]_D^{25}$ +13.03.

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Stereoselective Synthesis of 3-Fluoro Azetidinones *via* the Condensation of 2-Fluoropropanethioate Lithium Enolate with Imines

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Abstract: *S*-Phenyl 2-fluoropropanethioate (**1**) was treated with lithium diisopropylamide in THF at -78 °C to give rise to the lithium enolate, which underwent stereoselective condensation with a variety of aldehyde imines (**2**) at room temperature to afford the corresponding *trans*-3-fluoro-3-methyl-2-azetidinone derivatives (**3**) in fair to good yields.

INTRODUCTION

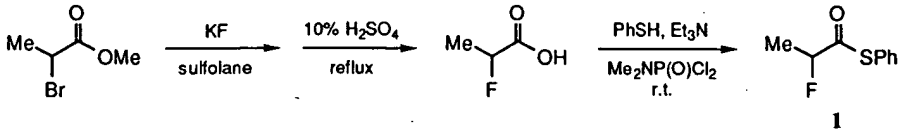
Since the discovery of the antibiotic activity of penicillin, thienamycin, and monobactams, a number of efforts have been made to develop efficient and stereoselective procedures for their preparations, many of which are based almost entirely upon the effective utilization of 2-azetidinone compounds as key intermediates.[1] According to the large volume of literature concerning with the synthesis of 2-azetidinones, the principal synthetic method for them is either the condensation reaction of ester enolates with imines[2] or the cycloaddition reaction of ketenes with imines.[3] The former ester enolate-imine condensation method has proved to be very useful for the construction, especially for diastereoselective or enantioselective construction, of the 2-azetidinone ring systems, as applied successfully to the synthesis of thienamycin or carbapenem antibiotics.[4]

In recent years, fluorine-containing 2-azetidinones have received increasing interest in the field of organic synthesis and bioorganic or biological chemistry, because they may be empolyed as building blocks for preparing fluorinated β-lactam antibiotics, carbohydrates, and amino acids, which often cause a unique and dramatic change in biological activities.[5] Although the literature has numerous reports on the synthesis of fluorine-containing 2-azetidinone derivatives,[6,7] only a few isolated examples deal with the preparation *via* the ester enolate-imine condensation method leading to 3-monofluorinated or 3,3-difluorinated 2-azetidinone compounds. For instance, Taguchi, *et al.* reported[6a] the synthesis of 3,3-difluoro-2-azetidinones by using the Reformatsky-type reaction of ethyl bromodifluoroacetate or methyl iododifluoroacetate with imines. Welch, *et al.* recently obtained the diastereomeric mixtures of 3-fluoro-2-azetidinone derivatives through the condensation reaction between the lithium enolate of 2,4,6-trimethylphenyl fluoroacetate and imines.[6b] Fujisawa, *et al.* demonstrated that the reaction of the triisopropoxytitanium enolate of *t*-butyl fluoroacetate with chiral imine proceeds in a highly stereoselective way to give optically active 3-fluoro-2-azetidinone.[6c]

As the control of stereochemistry is a central problem in organofluorine synthesis as well as in organic synthesis, it is of great importance to develop highly stereoselective methods for the synthesis of fluorinated compounds. In this paper, we would like to report that the lithium enolate of *S*-phenyl 2-fluoropropanethioate (**1**) reacts readily with a variety of aldehyde imines (**2**) at ambient temperature to produce stereoselectively the corresponding *trans*-3-fluoro-3-methyl-2-azetidinone derivatives (**3**) in fairly good yields.

RESULTS AND DISCUSSION

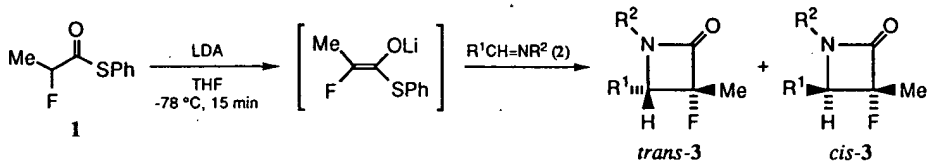
The starting thioester **1** was obtained according to such a three-step preparation as shown in Scheme 1. Thus, methyl 2-bromopropanoate was allowed to react with spray-dried potassium fluoride in tetramethylene sulfone (sulfolane) at 130 °C for 2.5 h, followed by distillation under reduced pressure to collect crude fluorinated methyl ester.[8,9] Hydrolysis of the crude ester with 10% sulfuric acid at reflux temperature for 1 h provided 2-fluoropropanoic acid in 52% overall yield. Thioesterification of this acid was readily made[10] by treating with benzenethiol and *N,N*-dimethylphosphoramidic dichloride[11] in the presence of triethylamine at room temperature for 2.5 h to give the desired *S*-phenyl thioester **1** in high yield.



1

Scheme 1. Preparation of *S*-Phenyl 2-Fluoropropanethioate (**1**)

When the thus obtained thioester **1** was allowed to react with lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78 °C for 15 min, followed by treatment with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) at the same temperature for 30 min, 1-(*t*-butyldimethylsilyl)oxy-2-fluoro-1-(phenylthio)-1-propene was obtained quantitatively as a mixture of the *E* and *Z* isomers (4 : 96). The stereochemistry of the predominant isomer was assigned as the *Z* configuration on the basis of relative comparison of its proton chemical shifts with those reported for the related fluorine-free ketene silyl acetals.[12] Thus, the intermediary lithium enolate of **1** was found to be generated stereoselectively with the *Z* configuration.[13]



1

trans-**3** *cis*-**3**

Scheme 2. Condensation of the Lithium Enolate of **1** with Imines **2**

The condensation reaction of this enolate with *N*-benzylideneaniline (**2a**) (R^1 = R^2 = Ph) was first examined under various conditions, as shown in Scheme 2. Table 1 summarizes the results of these reactions. The enolate of **1** did not react with **2a** (1.0 equiv.) at low temperature (-78 °C), resulting in the quantitative recovery of the starting thioester (Entry 1). The reaction was not so much improved as expected even by use of

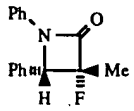
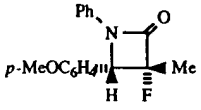
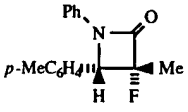
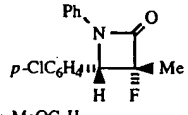
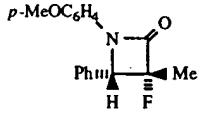
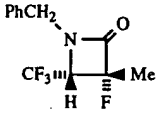
Table 1. Reaction of the Lithium Enolate of **1** with *N*-Benzylideneaniline (**2a**)

Entry	Imine **2a**/equiv.	Temp./°C	Time/h	Yield[a]/% of **3a**
1	1.0	-78	0.5	0
2	1.0	0	6.0	21
3	1.0	r.t.	4.0	53
4[b]	1.0	r.t.	4.0	23
5	1.0	r.t.	14.5	55
6	1.5	r.t.	4.0	73
7	1.5	r.t.	14.5	63
8	2.0	r.t.	14.5	61

[a] Yields refer to isolated product. [b] One equivalent of TMEDA was added prior to the reaction with **2a**.

higher reaction temperature (0 °C) and longer reaction period, *trans*-3-fluoro-3-methyl-1,4-diphenyl-2-azetidinone (**3a**) being produced only in 21% yield (Entry 2). The reaction performed at room temperature for 4.0 h (Entry 3) gave a 53% yield of **3a**, which was comparable to that obtained from the reaction at room temperature for 14.5 h (Entry 5). The addition of a coordinating solvent, such as *N,N,N',N'*-tetramethylethylenediamine (TMEDA), was quite ineffective for the present reaction (Entry 4). The use of 1.5 equiv. of imine **2a** substantially increased the yield of the product. On treating the lithium enolate of **1** with 1.5 equiv. of **2a** in THF at ambient temperature for 4 h, the corresponding 2-azetidinone **3a** was given in 73% yield (Entry 6).

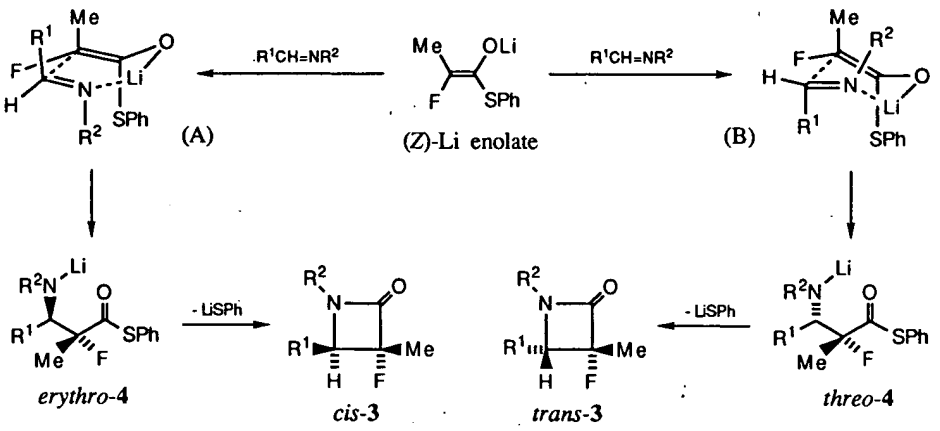
Table 2. Reaction of the Lithium Enolate of **1** with Various Imines **2**

Entry	Imine (2)		Product (3)		Yield[a] %	Isomer ratio[b] *trans* : *cis*
1	PhCH=NPh	(**2a**)		(**3a**)	73	>97 : <3
2	*p*-$MeOC_6H_4CH$=NPh	(**2b**)		(**3b**)	55	>97 : <3
3	*p*-MeC_6H_4CH=NPh	(**2c**)		(**3c**)	58	>97 : <3
4	*p*-ClC_6H_4CH=NPh	(**2d**)		(**3d**)	76	97 : 3
5	PhCH=NC_6H_4OMe-*p*	(**2e**)		(**3e**)	44	>97 : <3
6	CF_3CH=NCH_2Ph	(**2f**)		(**3f**)	44	>97 : <3

[a] Yields are of pure products isolated by column chromatography. [b] Determined by ^{19}F NMR.

Thus, the present reaction conditions were applied to the condensation reactions with other aldehyde imines **2** to synthesize a variety of 2-azetidinone derivatives **3**. Table 2 compiles the yields and isomer ratios of the products, together with their structures of the preferentially formed isomer. Various imines **2b-e** derived from aromatic aldehydes underwent the condensation with the lithium enolate of **1** leading to the corresponding 2-azetidinones **3b-e** in fair to good yields. Particularly, the imines carrying an electron-donating substituent, **2b** and **2c**, gave relatively lower yields of the products (Entries 2 and 3 in Table 2). This is probably due to decreased electrophilicity of their imino functionality. The imine prepared from an aliphatic aldehyde, such as *N*-butylidenepropylamine, failed to react at all. In contrast, the imine from trifluoroacetaldehyde **2f** participated in the reaction with the enolate of **1** to afford 4-trifluoromethylated 2-azetidinone **3f** in 44% yield (Entry 6 in Table 2).

Significantly, all the condensation reactions led to the exclusive formation of the *trans*-isomers[14] of **3**. No *cis*-isomers were present in amounts detectable by ^{19}F NMR, except for the reaction of **2d**. It should be noted, to our knowledge, that these reactions provide us with a precious example of the diastereoselective synthesis of fluorinated 2-azetidinones *via* an ester enolate-imine condensation method. The stereochemical assignment of **3** was made straightforward by ^{1}H and ^{19}F NMR. The spectra of 2-azetidinones **3a-f** showed vicinal H-F couplings in a range of 2.6-4.0 Hz, which are in good agreement with those reported[6b] recently for *trans*-3-fluoro-2-azetidinone compounds. In addition, the two isomers of 4-(4-chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (**3d**) could be isolated in the reaction of the lithium enolate with **2d**, their configurations being determined unambiguously; the major isomer bearing a vicinal H-F coupling of 3.6 Hz was assigned to be *trans*, while the minor isomer having a coupling of 12.0 Hz was determined to be *cis*.



Scheme 3. Possible Mechanism for the Formation of **3**

The formation of the 2-azetidinone ring system from an ester enolate and an imine is generally assumed to be multistage. The present reaction using the thioester enolate can also be explained by a quite analogous mechanism (Scheme 3). Thus, the first step, the aldol-type addition of the enolate to the imine **2**, gives rise to an acyclic aldolate-like β-amino thioester intermediate **4**. In the second step, this intermediate may undergo ring-closure followed by elimination of the phenylthio group to furnish the azetidinone product **3**. During the C-C bond formation in the addition step, two new stereogenic centers are formed and the stereochemistry of the final product is determined. Several reports[15] disclose that this addition step may be reversible and thus loss of stereoselectivity takes place *via* a retro-aldolization process. However, occurrence of such a process seems to be unlikely in the present reaction, because our failure to detect the intermediately formed β-amino thioesters **4** strongly suggests that the first step is much slower than the second step, and is irreversible. Another possibility is considered that an isomerization between the *E* and *Z* enolates results in decreasing or reversing the stereoselectivity of the reaction. But it may be ruled out by the fact that treatment of the lithium enolate of **1** with TBSOTf, after being left for 1-2 h at room temperature, gave a 4 : 96 mixture of the *E* and *Z* isomers of the silylated ketene acetal.

Keeping in mind these results combined with the *Z* configuration of the enolate of **1** as well as the *E* configuration[16] of most imines, we assume that the addition reaction is likely to proceed through a rigid cyclic chair- or boat-like transition state[17] with coordination of the imine **2** to the lithium ion of the enolate, as shown in Scheme 3. In the boat-like transition state (A), leading to the formation of the *cis*-2-azetidinone **3** *via erythro*-aldolate[18] intermediate **4**, an important 1,2-eclipsed nonbonded interaction can be observed between the methyl group of the enolate and the R^1 group of **2**. On the other hand, the chair-like transition state

(B) will scarcely have such destabilizing interactions and, therefore, is energetically more favorable than the transition state (A). Thus, the addition reaction between the enolate and imine **2** may occur through the chair-like transition state (B) to produce preferentially the *trans*-2-azetidinone **3**.

EXPERIMENTAL SECTION

General methods and materials. Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Shimadzu IR-400 spectrophotometer. ^{1}H NMR spectra were measured with Hitachi R-24B (60 MHz) NMR and/or General Electric QE-300 (300 MHz) FT-NMR spectrometers in a $CDCl_3$ solution with tetramethylsilane as an internal reference. A Hitachi R-24F (56.466 MHz) NMR spectrometer was used for determining ^{19}F NMR spectra in a $CDCl_3$ solution with external CF_3COOH. Proton and fluorine chemical shifts, downfield from the corresponding references, are expressed positive in parts per million (ppm). Mass spectra (MS) were taken on a Hitachi M-80 or a Shimadzu QP-1000 GC mass spectrometer operating at an ionization potential of 70 eV. Column chroma-tography was carried out on silica gel C-200 (100-200 mesh, Wako Pure Chemical Industries, Tokyo) with the indicated solvents. All reactions were performed under an atmosphere of dry argon. THF and 1,2-di-methoxyethane were distilled from lithium aluminum hydride or benzophenone ketyl. Other solvents were freshly distilled prior to use. Aldehydes, except 4-chlorobenzaldehyde, were distilled (or vacuum-distilled) from calcium hydride and stored under argon. 4-Chlorobenzaldehyde was purified by recrystallization from hexane. *N,N*-Dimethylphosphoramidic dichloride[11] was commercially available from Tokyo Chemical Industry Co., Ltd. A 1.6 *M* hexane solution of butyllithium was purchased from Aldrich Chemical Co., Inc. All chemicals are of reagent grade and, if necessary, were purified by a conventional manner before use.

Preparation of 2-fluoropropanoic acid. In a three-necked flask, equipped with a magnetic stirrer, a thermometer, and a still head for distillation, were placed methyl 2-bromopropanoate (41.75 g, 250 mmol), spray-dried potassium fluoride (21.46 g, 370 mmol), and sulfolane (75 mL). The mixture was heated with stirring at 130 °C for 2.5 h, followed by distillation under the pressure of 50-100 mmHg at 130-150 °C to collect crude methyl 2-fluoropropanoate (23.02 g). The crude ester was mixed with 10% sulfuric acid (500 mL) and the mixture was refluxed for 1 h. After being cooled to room temperature, this mixture was made saturated with sodium chloride and then was subjected to extraction with diethyl ether (50 mL x 10). The ethereal extracts were washed with brine, dried over anhydrous magnesium sulfate, and filtered. The filtrate was concentrated to leave a residual oil, which was distilled under reduced pressure to give pure 2-fluoropropanoic acid (11.96 g) in 52% overall yield. B.p. 86.0-87.0 °C (35 mmHg); IR (film) 3680-2783 (br s), 3003 (s), 2950 (m), 1740 (vs), 1470 (m), 1457 (m), 1380 (m), 1240 (m), 1125 (s), 1100 (s), 1049 (m), 826 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.63 (dd, J = 7.3 and 23.0 Hz, 3H), 5.01 (dq, J = 48.0 and 7.3 Hz, 1H), 11.57 (s, 1H); ^{19}F NMR ($CDCl_3$) δ -106.0 (dq, J = 48.0 and 23.0 Hz, 1F).

Preparation of S-phenyl 2-fluoropropanethioate (1). To a stirred solution of 2-fluoropropanoic acid (1.85 g, 20 mmol) in 1,2-dimethoxyethane (110 mL) were added successively triethylamine (4.85 g, 48 mmol), *N,N*-dimethylphosphoramidic dichloride (3.89 g, 24 mmol), and benzenethiol (2.64 g, 24 mmol) at such a rate that the reaction temperature did not rise above 10 °C. After stirring at ambient temperature for 2.5 h, the mixture was poured into a cold 5% HCl solution and was extracted with chloroform (70 mL x 4). The organic extracts were dried over sodium sulfate, followed by filtration and concentration. The residue was chromatophraphed on a silica-gel column using hexane and benzene as eluents to afford *S*-phenyl 2-fluoropropanethioate (**1**) in 84% yield. M.p. 44.2-45.0 °C; IR (KBr) 3057 (w), 2937 (w), 1704 (vs), 1584 (w), 1482 (s), 1444 (s), 1373 (m), 1319 (m), 1148 (s), 1086 (s), 1068 (s), 1020 (m), 976 (vs), 870 (s), 743 (vs), 706

(s), 686 (vs) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.60 (dd, J = 6.8 and 23.6 Hz, 3H), 5.03 (dq, J = 47.8 and 6.8 Hz, 1H), 7.32 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -114.5 (dq, J = 47.8 and 23.6 Hz, 1F); MS *m/z* (rel. intensity) 184 (M^+, 45), 110 (100).

Preparation of imines (2). *N*-Benzylideneaniline (**2a**), *N*-(4-methoxybenzylidene)aniline (**2b**), *N*-(4-methylbenzylidene)aniline (**2c**), *N*-(4-chlorobenzylidene)aniline (**2d**), *N*-benzylidene-4-methoxyaniline (**2e**), *N*-(2,2,2-trifluoroethylidene)benzylamine (**2f**), and *N*-butylidenepropylamine were prepared according to the literature method.[19]

Reaction of the lithium enolate of S-phenyl 2-fluoropropanethioate (1) with t-butyldimethylsilyl trifluoromethanesulfonate. Lithium diisopropylamide was prepared by the reaction of diisopropylamine (0.222 g, 2.2 mmol) with a 1.6 *M* hexane solution of butyllithium (1.38 mL, 2.2 mmol) in THF (5.5 mL) at 0 °C for 0.5 h. To this solution was dropwise added a solution of **1** (0.368 g, 2.0 mmol) in THF (1 mL) at -78 °C. The mixture was stirred for 15 min at -78 °C and then TBSOTf (1.109 g, 4.2 mmol) was added to it. After stirring at -78 °C for 0.5 h, the reaction was quenched with an aqueous ammonium chloride solution and the resulting mixture was extracted with diethyl ether (25 mL x 4). The extracts were washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Thorough removal of volatile materials from the residue provided 1-(*t*-butyldimethylsilyl)oxy-2-fluoro-1-(phenylthio)-1-propene (0.584 g) quantitatively in an almost pure form. The isomer ratio of this silylated product was measured by ^{19}F and ^1H NMR as *E* : *Z* = 4 : 96. IR (film) 3056 (w), 2954 (s), 2923 (s), 2858 (m), 1588 (w), 1485 (m), 1467 (m), 1446 (m), 1252 (s), 1191 (vs), 1172 (vs), 1088 (m), 1024 (m), 852 (vs), 840 (vs), 781 (s), 736 (s), 685 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.13 (s, 6H), 0.89 (s, 9H), 2.09 (d, J = 15.8 Hz, 3H) for the *Z* isomer, 2.14 (d, J = 16.2 Hz, 3H) for the *E* isomer, 7.18 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -27.0 (d, J = 16.2 Hz, 1F) for the *E* isomer, -38.2 (d, J = 15.8 Hz, 1F) for the *Z* isomer.

Reaction of the lithium enolate of S-phenyl 2-fluoropropanethioate (1) with various imines (2). The reaction of the lithium enolate of **1** with *N*-benzylideneaniline (**2a**) was described as the typical procedure. To a THF solution of lithium diisopropylamide (2.2 mmol) was gradually added a solution of **1** (0.368 g, 2.0 mmol) in THF (1 mL) at -78 °C under argon. After stirring for 15 min at the same temperature, a solution of **2a** (0.543 g, 3.0 mmol) in THF (1 mL) was dropwise added to the reaction mixture. The whole was stirred for 4 h at room temperature and then poured into a cold aqueous ammonium chloride solution. The resultant mixture was extracted with diethyl ether (25 mL x 3) and with chloroform (25 mL x 2). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was chromatographed on silica gel with hexane-benzene (1:2) and benzene to furnish analytically pure product **3a** (0.373 g) in 73% yield.

trans-3-Fluoro-3-methyl-1,4-diphenyl-2-azetidinone (3a). M.p. 154.3-154.7 °C; IR (KBr) 3032 (w), 2988 (w), 1744 (vs), 1600 (m), 1498 (s), 1460 (m), 1391 (s), 1366 (m), 1206 (m), 1149 (m), 1114 (s), 1080 (w), 1050 (m), 1027 (w), 960 (w), 898 (w), 843 (w), 825 (w), 766 (m), 750 (s), 683 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.77 (d, J = 22.0 Hz, 3H), 4.97 (d, J = 3.6 Hz, 1H), 7.0-7.4 (m, 5H), 7.31 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -82.5 (dq, J = 3.6 and 22.0 Hz, 1F); MS *m/z* (rel. intensity) 255 (M^+, 0.9), 136 (100). HRMS (EI) Found: *m/z* 255.1068. Calcd for $C_{16}H_{14}FNO$: M, 255.1060.

trans-3-Fluoro-4-(4-methoxyphenyl)-3-methyl-l-phenyl-2-azetidinone (3b). Eluted with hexane-ethyl acetate (5:1); 55% yield; m.p. 111.7-113.2 °C; IR (KBr) 3006 (w), 2973 (w), 2925 (w), 2845 (w), 1753 (vs), 1618 (s), 1600 (s), 1587 (m), 1500 (vs), 1469 (m), 1452 (m), 1425 (w), 1385 (vs), 1339 (m), 1308 (s), 1293 (s), 1251 (vs), 1215 (m), 1203 (m), 1172 (s), 1124 (vs), 1083 (m), 1053 (w), 1020 (s), 954 (m), 840 (s), 816 (s), 785 (m), 757 (vs), 740 (m), 683 (s), 670 (w), 650 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (d, J = 21.8 Hz,

3H), 3.72 (s, 3H), 4.89 (d, J = 4.0 Hz, 1H), 6.80 (ABq, J = 9.2 Hz, 2H), 7.0-7.3 (m, 2H and 5H); ^{19}F NMR ($CDCl_3$) δ -83.0 (dq, J = 4.0 and 21.8 Hz, 1F); MS *m/e* (rel. intensity) 285 (M^+, 1.8), 166 (100). HRMS (EI) Found: *m/z* 285.1164. Calcd for $C_{17}H_{16}FNO_2$: M, 285.1165.

trans-3-Fluoro-3-methyl-4-(4-methylphenyl)-1-phenyl-2-azetidinone (3c). Eluted with hexane-ethyl acetate (10:1); 58% yield; m.p. 138.2-139.4 °C; IR (KBr) 3030 (w), 2973 (m), 2918 (m), 2857 (w), 1740 (vs), 1601 (s), 1492 (s), 1465 (m), 1410 (w), 1376 (vs), 1311 (m), 1300 (m), 1206 (m), 1180 (m), 1160 (s), 1117 (s), 1077 (s), 1049 (m), 806 (s), 768 (m), 751 (vs), 731 (s), 683 (s), 651 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.76 (d, J = 22.0 Hz, 3H), 2.32 (s, 3H), 4.93 (d, J = 2.6 Hz, 1H), 7.14 (s, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -82.6 (dq, J = 2.6 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 269 (M^+, 4.2), 150 (100). HRMS (EI) Found: *m/z* 269.1200. Calcd for $C_{17}H_{16}FNO$: M, 269.1216.

trans-4-(4-Chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (3d). Eluted with hexane-benzene (1:2) and benzene; 76% yield; m.p. 153.9-154.9 °C; IR (KBr) 3032 (w), 2978 (w), 1748 (vs), 1600 (s), 1492 (s), 1467 (m), 1416 (m), 1377 (vs), 1297 (w), 1205 (m), 1161 (m), 1112 (s), 1083 (s), 1057 (m), 1014 (m), 850 (m), 806 (s), 789 (m), 751 (vs), 733 (s), 685 (w) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, J = 22.0 Hz, 3H), 4.97 (d, J = 3.6 Hz, 1H), 7.2-7.3 (m, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -82.4 (dq, J = 3.6 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 291 (M^++2, 1.7), 289 (M^+, 5.2), 170 (100). HRMS (EI) Found: *m/z* 289.0668. Calcd for $C_{16}H_{13}ClFNO$: M, 289.0671.

cis-4-(4-Chlorophenyl)-3-fluoro-3-methyl-1-phenyl-2-azetidinone (3d). Eluted with hexane-benzene (1:2); ^{1}H NMR ($CDCl_3$) δ 1.06 (d, J = 23.6 Hz, 3H), 5.12 (d, J = 12.0 Hz, 1H), 7.2-7.3 (m, 4H and 5H); ^{19}F NMR ($CDCl_3$) δ -71.8 (dq, J = 12.0 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 291 (M^++2, 1.7), 289 (M^+, 5.2), 170 (100).

trans-3-Fluoro-1-(4-methoxyphenyl)-3-methyl-4-phenyl-2-azetidinone (3e). Eluted with hexane-ethyl acetate (5:1); 44% yield; m.p. 147.2-148.4 °C; IR (KBr) 3062 (w), 3017 (w), 2968 (w), 2930 (w), 2835 (w), 1742 (vs), 1593 (w), 1518 (s), 1450 (s), 1403 (m), 1368 (m), 1322 (w), 1306 (s), 1250 (vs), 1212 (s), 1164 (s), 1120 (vs), 1031 (vs), 962 (m), 843 (vs), 829 (s), 808 (vs), 767 (m), 700 (s), 667 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, J = 22.0 Hz, 3H), 3.36 (s, 3H), 4.90 (d, J = 3.4 Hz, 1H), 6.69 and 7.18 (ABq, J = 8.4 and 8.4 Hz, 2H and 2H), 7.26 (s, 5H); ^{19}F NMR ($CDCl_3$) δ -82.3 (dq, J = 3.4 and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 285 (M^+, 10), 149 (100). HRMS (EI) Found: *m/z* 285.1165. Calcd for $C_{17}H_{16}FNO_2$: M, 285.1166.

trans-1-Benzyl-3-fluoro-3-methyl-4-(trifluoromethyl)-2-azetidinone (3f). Eluted with hexane-chloroform (1:1); 44% yield; IR (film) 3053 (w), 3011 (w), 2975 (w), 2922 (w), 1780 (vs), 1601 (w), 1583 (w), 1496 (w), 1451 (m), 1440 (m), 1400 (vs), 1380 (s), 1350 (m), 1289 (vs), 1175 (vs), 1111 (s), 1084 (s), 1070 (s), 952 (m), 940 (m), 860 (m), 831 (m), 735 (m), 694 (vs), 666 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.61 (d, J = 22.0 Hz, 3H), 3.65 (dq, J = 3.0 and 5.8 Hz, 1H), 3.96 (d, J = 13.4 Hz, 1H), 4.71 (d, J = 13.4 Hz, 1H), 7.0-7.5 (m, 5H); ^{19}F NMR ($CDCl_3$) δ 8.0 (dd, J = 5.8 and 13.5 Hz, 3F), -85.9 (dqq, J = 3.0, 13.5, and 22.0 Hz, 1F); MS *m/e* (rel. intensity) 261 (M^+, tr), 91 (100). HRMS (CI) Found: *m/z* 262.0848. Calcd for $C_{12}H_{11}F_4NO$: M+H, 262.0855.

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13. High *erythro*-selectivity[18] observed in the aldol reaction of the lithium enolate of **1** with benzaldehyde affords an additional support for the present stereochemical assignment of the enolate. Details of the diastereoselective aldol reaction with aldehydes will be reported elsewhere.
14. The *trans* and *cis* designations are made by specifying the relative positions of similar substituent groups. Thus, the *trans* configuration is assigned to the isomer of **3** in which the carbon groups, methyl and R^1, are *trans* to each other.
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Synthesis of a Novel Fluoro-tribactam Utilising an *N*-Fluorosulf nimide in the key step

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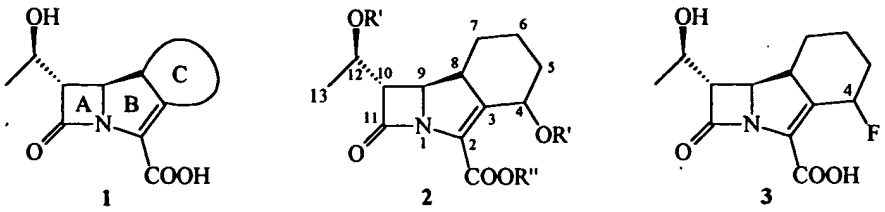
Abstract: The electrophilic reagent *N*-fluorobenzenesulfonimide (NFSI) was used in the synthesis of the α-fluoro ketone **7**, a key intermediate for the synthesis of the β-lactam **13**. This highly reactive fluorinated tribactam **13** was rapidly hydrolysed in aqueous solution.

Introduction

The introduction of fluorine into biologically active compounds has been widely investigated since it alters the physico-chemical properties of the molecule and can potentiate biological activity.[1,2] The substitution of hydrogen with fluorine does not affect the steric demand of the molecule. In fact, the Van der Waals radii of hydrogen (1.10 Å) and fluorine (1.36 Å), and therefore the C-H (1.08-1.11 Å) and C-F (1.26-1.41 Å) bond lengths, are very similar.[1] However, the electron distribution within the molecule will be affected due to the high electronegativity of fluorine. In addition the lipophilicity of the fluorinated compound is greatly enhanced.[2] Finally fluoride is also a good leaving group in E_2 elimination reactions and this can be influential when such a mechanism is involved in the *in situ* formation of an enzyme inhibitor.

In recent years the synthesis of fluorinated derivatives of non-classical β-lactam antibacterial agents, such as the carbapenems, has received particular attention. In this context, Shah and Cama prepared 1,1-difluorocarbapenem in order to accentuate the reactivity of the β-lactam ring.[3] However, due to its enhanced reactivity, this compound could not be tested as an antibacterial agent.[3] In a related study Watanabe and co-workers prepared a series of 8-fluorocarbapenem derivatives.[4] The most interesting result was the improvement of the water solubility of the fluorinated compounds compared to imipenem (ratio *ca* 30 : 1), (a major drawback of imipenem in the clinic is that its use is restricted to infusion).[5] Fukumoto *et al* published the synthesis of potentially useful intermediates for 1-fluorocarbapenems by coupling of 4-acetoxy-2-azetidinone and the lithium enolate of dimethyl fluoromalonate.[6] Furthermore 3-fluoro substituted β-lactams have been prepared by Welch *et al* using the ketene-imine condensation[7] and by Fuchigami and co-workers *via* anodic monofluorination of 2-aryl-4-thiazolidinones followed by oxidation of the fluorinated heterocycle to the corresponding sulfones followed by thermal ring contraction.[8] Glaxo S. p. A. recently discovered a new family of synthetic β-lactam antibiotics, the tribactams **1**, possessing a tricyclic skeleton.[9] In connection with the preparation of compounds in this series we have shown that radical coupling of 4-phenylselenoazetidin-2-one

with some 2-substituted cyclohexenones yields 2,6-*cis*-substituted cyclohexanones, after rearrangement of the initially formed species. This methodology was used as the key step in the synthesis of the tribactam of type **2**.[10]

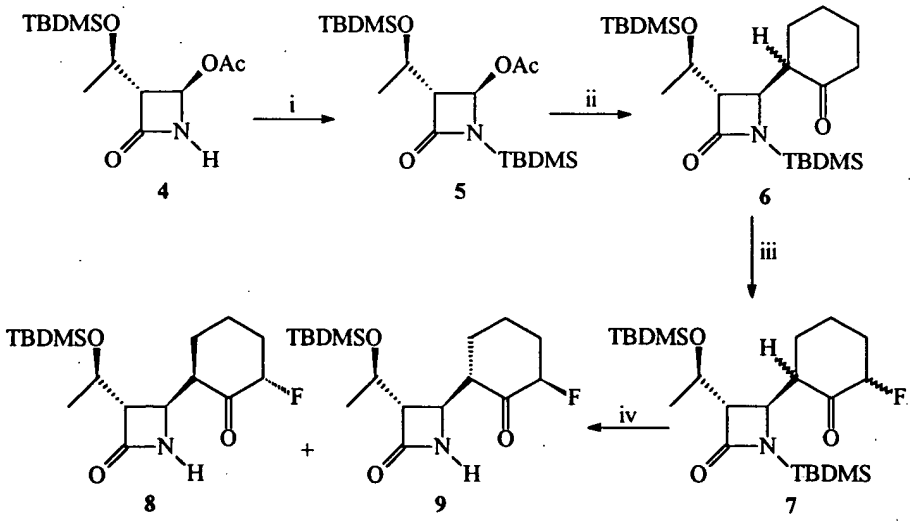


In order to extend the range of electron withdrawing and/or nucleofugic substituents at the C-4 position within the tricyclic molecule, we set out to prepare the 4-fluoro substituted tribactam **3**.[11]

Results and Discussion

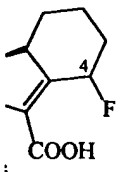
Commercially available 4-acetoxy-azetidin-2-one **4** was *N*-protected using standard conditions (Scheme 1). Coupling of the 4-acetoxy β-lactam **5** with 1-trimethylsilyloxycyclohexene mediated by tin(IV) chloride afforded the α-substituted ketone **6** as a mixture of two diastereoisomers in the ratio 7 : 3.

The key step in this synthesis involved the use of an electrophilic fluorinating reagent,[12] *N*-fluorobenzene sulfonimide (NFSI). The latter compound is an easy-to-handle, stable white crystalline solid and has been used heretofore to fluorinate lithium enolates.[12] We were very pleased to find that treatment of the ketone **6** with $LiN(SiMe_3)_2$ followed by addition of NFSI at low temperature afforded the α-fluorinated ketone **7** as a mixture of two diastereoisomers (ratio 7 : 3) in excellent yield. In both isomers the substituents at C-2 and C-6 in the cyclohexanone ring were *trans* oriented.



Scheme 1 *Reagents and Conditions* : i, Et_3N, TBDMSCl, CH_2Cl_2, 88 %; ii, $SnCl_4$, CH_3CN, 1-trimethylsilyloxycyclohexene, 75 %; iii, $LiN(SiMe_3)_2$, $FN(PhSO_2)_2$, THF, -78°C, 95 %; iv, NH_4F, MeOH, 90%.

rearrangement of the
tribactam of type 2.[10]



ıe C-4 position within

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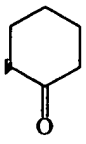
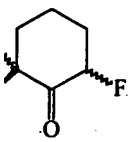


TBDMS



TBDMS
7

$SnCl_4$, CH_3CN, 1-
NH_4F, MeOH, 90%.

N-Desilylation using ammonium fluoride in methanol afforded the ketones **8** and **9** (90 % yield). Relevant nOe's that allowed an allocation of structure 8 and 9 to the major and minor isomers respectively are shown in the Figure 1. Note that for both isomers, no nOe's were observed between the 2' and 6' protons, denoting an *anti*-axial-equatorial relationship between these two protons.

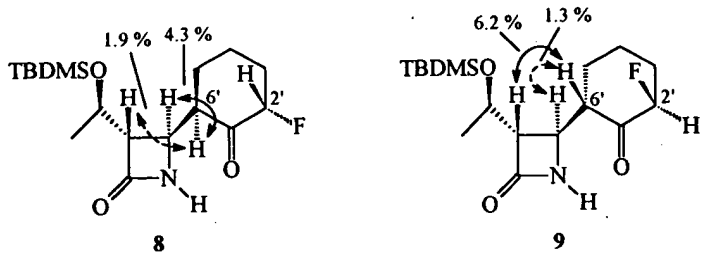
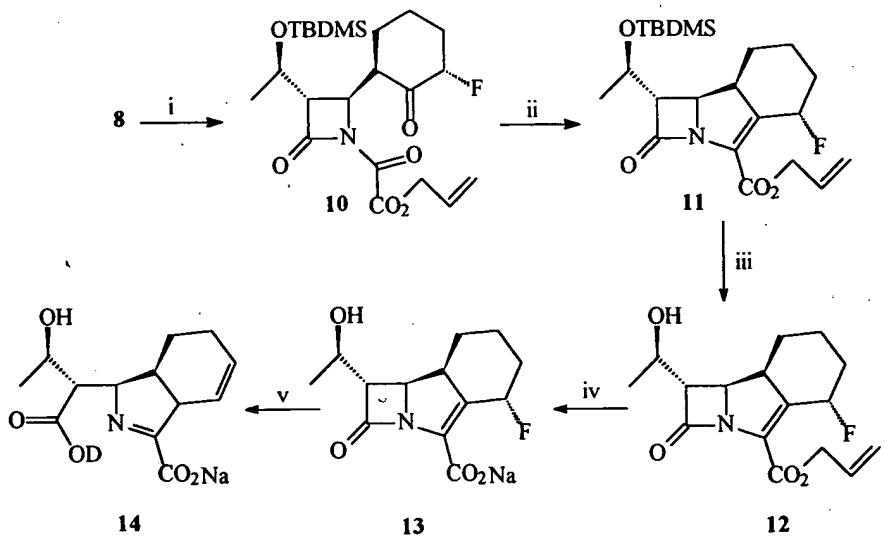


Figure 1

The 2'*S*, 6'*R* isomer **8** was *N*-acylated with allyl oxalyl chloride in the presence of triethylamine in xylene to give the oxalimide **10** (Scheme 2), which was transformed *in situ* into the tricyclic structure **11** *via* an intramolecular Wittig-type cyclization[13] (triethyl phosphite, xylene, reflux, 67 %). Compound **11** was deprotected in standard fashion to give the alcohol **12**. Palladium catalysed deallylation[14] of the ester furnished the carboxylate **13** as the sodium salt in 90 % yield. The tribactam **13** was rapidly hydrolysed in D_2O (as shown by ^1H NMR), with consequent elimination of the fluorine atom to afford the imino acid salt **14**.



Scheme 2 *Reagents and Conditions* : i, Et_3N, $ClCOCO_2CH_2CHCH_2$, xylene, 0°C; ii, $P(OEt)_3$, xylene, 140°C, 67 %; iii, AcOH, TBAF, THF, 65 %; iv, $Pd(PPh_3)_4$, PPh_3, Na-2-ethylhexanoate, THF, 90 %; v, D_2O, 30 min.

Further studies on the conversion **13** ⇒ **14** are in progress and will be reported in due course. Microbiological testing of the tribactam **13** was not possible as activity assays are run in aqueous solution over 18 hours. However the mode of ring-opening of the fluoro-compound **13** may give an indication of the mechanism of action of other compounds in the tribactam series. Thus the nucleofugicity of the substituent at C-4 in the tribactam must be attenuated to provide a good "sink" for negative charge after nucleophilic opening of the β-lactam ring (*cf* the parallel situation with the cephalosporin series, Figure 2). The nucleofuge should be lost

readily following attack on the tribactam by the serine-based nuclephile of the target transpeptidase but should not be so highly active as to precipitate attack on the β-lactam carbonyl group by other, weaker nucleophiles, such as water.

Tribactam **Cephalosporin**

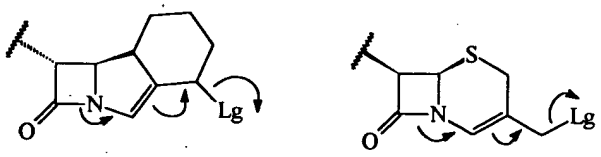


Figure 2

Acknowledgements

We wish to thank Dr. V. Šik (University of Exeter) for NMR experiments and Mr. E. Underwood (University of Exeter) for mass spectral data. We thank Glaxo S. p. A. for a research studentship to A. Padova.

Experimental Section

General. - IR spectra were recorded on a Perkin-Elmer 881 spectrometer. Absorption maxima were recorded in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 250 MHz and/or a Bruker AC 300 spectrometer operating at 300 MHz. ^{13}C NMR spectra were recorded on a Bruker AM 250 spectrometer operating at 62.9 MHz or a Bruker AC 300 spectrometer operating at 75.4 MHz. 400 and 500 MHz ^1H NMR Spectra were recorded at Glaxo S.p.A., Verona, Italy. All chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are quoted in Hz. Mass spectra were recorded on a Kratos Profile instrument. Fast atom bombardment (FAB) spectra were recorded at Glaxo S.p.A. (Verona, Italy) using a V.G.Quattro instrument. Optical rotations were measured on a AA-1000 polarimeter. Melting points were determined on a Gallenkamp capillary apparatus and are uncorrected. Reagents were used as supplied, with the exception of the following which were purified as described : -
triethylamine, distilled from and onto, potassium hydroxide pellets; 1,1,1,3,3,3-hexamethyldisilazane, distilled from and onto, potassium hydroxide pellets; *N*-fluorobenzene sulphonimide, purified by column chromatography (CH_2Cl_2).
Light petroleum refers to the fraction of b.p. 40-60°C and was distilled prior to use. Ethyl acetate was distilled prior to use. Ether and tetrahydrofuran were distilled from sodium using benzophenone ketyl radical as indicator. Dichoromethane was distilled from calcium hydride. Xylene was dried over sodium wire. TLC was performed using pre-coated glass plates (Merck silica gel 60F 254). The plates were visualised using UV light (254 nm) and/or phosphomolybdic acid in ethanol, or ninhydrin in ethanol/hydrochloric acid. Flash chromatography was performed using Merck silica 60 (40-63 μm).

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-4-acetoxy-3[(*R*)-(*tert*-butyldimethyl-silyloxy)-ethyl]-2-azetidinone (5) (3*S*,4*R*)-4-Acetoxy-3[(*R*)-(*tert*-butyldimethylsilyloxy)ethyl]-2-azetidinone (**4**) (14.37 g, 50 mmol) and *tert*-butyldimethylsilylchloride (11.3 g, 75 mmol) were dissolved in anhydrous dichloromethane (100 cm^3) and the reaction mixture cooled down to 0°C. Triethylamine (10.4 cm^3, 75 mmol) was then added. The reaction mixture was stirred at 0°C for 2 h and then allowed to warm up to room temperature. After stirring for 30 h, the mixture was poured into water (75 cm^3) and extracted with dichloromethane (2 x 100 cm^3). The combined organic extracts were washed with brine (75 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue was purified by column chromatography (CH_2Cl_2) to give the β-lactam (**5**), produced as a yellow oil (17.74 g, 88%); $[\alpha]_D^{25}$ -35 (c = 1, $CHCl_3$), ν_{max} ($CHCl_3$)/cm^{-1} 1767 (C=O, β-lactam) and 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 0.03 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.16 (3H, s, $SiCH_3$), 0.23 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 0.93 (9H, s, $SiC(CH_3)_3$), 1.23 (3H, d, *J* 6.2, CH_3), 2.04 (3H, s, CH_3CO), 3.10 (1H, d, $J_{3,4\ trans}$ 1.5, *J* 3.0, 3-H), 4.18 (1H, m, CH_3CH), 6.17 (1H, d, $J_{4,3\ trans}$ 1.5, 4-H); δ_C (75.5 MHz, $CDCl_3$) -6.44 ($SiCH_3$), -5.77 ($SiCH_3$), -4.80 ($SiCH_3$), -4.68 ($SiCH_3$), 17.91(SiC), 17.94 (SiC), 21.10 ($CHCH_3$), 22.10

(COCH$_3$), 25.78 (SiC(CH$_3$)$_3$), 25.87 (SiC(CH$_3$)$_3$), 64.10 (3-CH), 67.58 (CH$_3$CH), 76.44 (4-CH), 169.52 (C=O), 171.05 (C=O). LRMS (EI) : m/z 344 [M-C(CH$_3$)$_3$]$^+$ (48%), 302 [M+H-COCH$_3$-C(CH$_3$)$_3$]$^+$ (80%), 242 [M-CH$_3$CH(OTBDMS)]$^+$ (11%), 87 [M+H-TBDMS-CH$_3$CH(OTBDMS)CHC=O]$^+$ (100%).
HRMS (EI) Found: [M]$^+$ 401.24000. $C_{19}H_{39}NO_4Si_2$ requires M 401.24176.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*R*)-1′-oxocyclohex-2′-yl]-2-azetidinone and **(3*S*,4*R*)-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*S*)-1′-oxocyclohex-2′-yl]-2-azetidinone (6).** Tin tetrachloride (8 cm^3, 68 mmol) was added dropwise to a solution of acetonitrile at -35°C. The reaction mixture was allowed to warm up to 5°C and then a mixture of β-lactam (**5**) (20 g, 50 mmol) and 1-cyclohexenyloxytrimethylsilane (15.2 cm^3, 100 mmol) in acetonitrile (60 cm^3) was added to the mixture at 10°C. After 1 h, the reaction mixture was poured into a mixture of 0.4M sodium hydroxide (800 cm^3) and diethyl ether (300 cm^3). After stirring for 15 min, the organic phase was washed with water (2 x 100 cm^3) until neutral by pH indicator paper, then brine (100 cm^3) and dried (MgSO$_4$). The solvent was evaporated under vacuum and the crude product (23.5 g) was dissolved in isopropyl alcohol (75 cm^3) at 40°C. Water (75 cm^3) was added until a solid crystallised out of solution. After stirring for 15 min, the solid was filtered off and washed with a ice-cold mixture of isopropyl alcohol and water (1 : 2) (20 cm^3). The product was dissolved in diethyl ether (150 cm^3), washed with brine (50 cm^3), dried (MgSO$_4$) and the solvent was evaporated under vacuum to give the mixture of azetidinones (**6**), obtained as a white solid (14.2 g, 63%) (mixture of two diastereoisomers in the ratio 7 : 3). δ_H (300 MHz, CDCl$_3$) 0.03 (3H, s, SiCH$_3$), 0.04 (3H, s, SiCH$_3$), 0.05 (3H, s, SiCH$_3$), 0.06 (3H, s, SiCH$_3$), 0.07 (3H, s, SiCH$_3$), 0.17 (3H, s, SiCH$_3$), 0.20 (3H, s, SiCH$_3$), 0.24 (3H, s, SiCH$_3$), 0.84 (9H, s, SiC(CH$_3$)$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.94 (18H, s, 2 x SiC(CH$_3$)$_3$), 1.22 (3H, d, *J* 6.2, CH$_3$), 1.24 (3H, d, *J* 6.2, CH$_3$), 1.40-1.74 (5H, m), 1.90-2.14 (5H, m), 2.16-2.44 (5H, m), 2.52-2.64 (2H, m), 2.90 (1H, dd, *J* 3.0, $J_{3,4\ trans}$ 4.5, 3-H), 3.24 (1H, dd, $J_{3,4\ trans}$ 3.0, *J* 7.5, 3-H), 3.97 (1H, t, $J_{4,3\ trans}$ 2.5, $J_{4,2'\ cis}$ 2.5, 4-H), 4.05 (1H, m, CH$_3$CH), 4.13 (1H, dd, $J_{4,3\ trans}$ 2.5, $J_{4,2'\ trans}$ 4.5, 4-H), 4.20 (1H, m, CH$_3$CH); δ_C (75.5 MHz, CDCl$_3$) -5.45 (SiCH$_3$), -5.13 (SiCH$_3$), -5.04 (SiCH$_3$), -4.73 (SiCH$_3$), -4.67 (SiCH$_3$), -4.51 (SiCH$_3$), -4.43 (SiCH$_3$), -4.34 (SiCH$_3$), 17.90 (SiC), 18.04 (SiC), 18.39 (SiC), 18.87 (SiC), 21.94 (CH$_3$), 22.86 (CH$_3$), 24.96 (CH$_2$), 25.03 (CH$_2$), 25.80 (SiC(CH$_3$)$_3$, 25.94 (SiC(CH$_3$)$_3$), 26.24 (SiC(CH$_3$)$_3$), 26.36 (SiC(CH$_3$)$_3$), 26.89 (CH$_2$), 27.61 (CH$_2$), 28.54 (CH$_2$), 28.91 (CH$_2$), 42.30 (CH$_2$), 42.35 (CH$_2$), 50.67 (2′-CH), 52.16 (2′-CH), 52.67 (3-CH), 53.65(3-CH), 60.58 (4-CH), 62.07 (CH$_3$CH), 66.01 (4-CH), 67.64 (CH$_3$CH), 173.54 (N-C=O), 173.82 (N-C=O), 209.58 (1′-C=O), 210.46 (1′-C=O). LRMS (EI) : m/z 382 [M-C(CH$_3$)$_3$]$^+$ (76%), 182 [M-CH$_3$CH(OTBDMS)CHC=O-C(CH$_3$)$_3$]$^+$ (11%), 75 [(CH$_3$)$_2$SiOH] (100%). HRMS (EI) Found: [M]$^+$ 439.29501. $C_{23}H_{45}NO_3Si_2$ requires M 439.29380.

(3*S*,4*R*)-1-(*tert*-Butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*R*,6′*S*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone and ***S*,4*R*)-1-(*tert*-butyldimethylsilyl)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)-ethyl]-4-[(2′*S*,6′*R*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (7).** *n*-BuLi (2.5 M in hexane) (0.56 cm^3, 1.4 mmol) was added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.295 cm^3, 1.4 mmol) in THF (5 cm^3) at -78°C. After 30 min at -78°C, a mixture of β-lactams (**6**) (7 : 3) (0.439, 1 mmol) in THF (5 cm^3) was cannulated in the reaction vessel. The mixture was allowed to warm up to -50°C. After 30 min, the mixture was cooled down to -78°C. *N*-Fluorobenzene sulphonimide (0.441, 1.4 mmol) in THF (2 cm^3) was then added and the mixture was allowed to warm up to -30°C. After stirring for 30 min at -30°C, saturated ammonium chloride solution (10 cm^3) was carefully added to the reaction mixture which was then extracted with ethyl acetate (2 x 75 cm^3). The organic phase was stirred with 10% aqueous sodium thiosulphate (50 cm^3) for 30 min, washed with 10% aqueous sodium hydrogen carbonate solution (2 x 50 cm^3), brine (50 cm^3) and dried (MgSO$_4$). The solvent was evaporated under vacuum and the residue purified by column chromatography [ethyl acetate / light petroleum (b.p. 40-60°C) (1 : 4)] to yield the fluorinated ketone (**7**) as a mixture of two inseparable isomers in the ratio 7 : 3. The ketone (**7**) was obtained as a white residue (0.435 g, 95%). A sample of pure (2′α,6′β) diastereoisomer was obtained by repeated column chromatography purification. ν_{max} neat/cm^{-1} 1745 (C=O); δ_H (250 MHz, CDCl$_3$) 0.08 (3H, s, SiCH$_3$), 0.09 (3H, s, SiCH$_3$), 0.13 (3H, s, SiCH$_3$), 0.14 (3H, s, SiCH$_3$), 0.80 (9H, s, SiC(CH$_3$)$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 1.25 (3H, d, *J* 6.2, CH$_3$), 1.45-2.00 (6H, m), 2.92 (1H, dd, $J_{3,4\ trans}$ 2.5, *J* 5.5, 3-H), 3.18 (1H, m, $J_{6',4}$ 5.5, 6′-H), 4.08 (1H, dd, $J_{4,3\ trans}$ 2.5, $J_{4,6'\ cis}$ 5.5, 4-H), 4.18 (1H, m, CH$_3$CH), 4.75 (1H, ddd, *J* 2.0, *J* 4.5, $J_{H,F}$ 51.5, 2′-H); δ_C (75.5 MHz, CDCl$_3$) -5.35 (SiCH$_3$), -4.93 (SiCH$_3$), -4.64 (SiCH$_3$), -4.31 (SiCH$_3$), 18.01 (SiC), 18.41 (SiC), 19.48 (4′-CH$_2$, d, *J* 2.5), 22.30 (CHCH$_3$),

25.92 ($SiC(CH_3)_3$), 26.25 ($SiC(CH_3)_3$), 30.76 (5′-CH_2), 34.21 (3′-CH_2, d, *J* 22), 50.44 (3-CH), 50.88 (6′-CH, d, *J* 2), 61.00 (4-CH), 66.29 (CH_3CH), 93.37 (2′-CH, d, *J* 180), 173.55 (N-C=O), 207.54 (C=O, d, *J* 21.8).
LRMS (EI) : m/z 400 $[M-C(CH_3)_3]^+$ (67%), 285 $[M-TBDMS-C(CH_3)_3]^+$ (3%), 242 $[M-CH_3-CH(OTBDMS)-C(CH_3)_3]^+$ (14%), 159 $[CH_3CH(OTBDMS]^+$ (100%). HRMS (EI) Found: $[M]^+$ 457.28380. $C_{23}H_{44}FNO_3Si_2$ requires M 457.28436.

(3*S*,4*R*)-3-[(*R*)-1-(*tert*-Butyldimethylsilyloxy)ethyl]-4-[(2′*R*,6′*S*)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (9) and (3*S*,4*R*)-3-[(*R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-4-[(2′S,6′R)-(2′-fluoro-1′-oxocyclohex-6′-yl)]-2-azetidinone (8). The ketone (7) (0.1 g, 0.218 mmol) was dissolved in anhydrous methanol (2.5 cm^3). Ammonium fluoride (0.009 g, 0.261 mmol) was added and the mixture was stirred for 30 min. The solvent was then evaporated under vacuum and the residue was purified by column chromatography [ethyl acetate / light petroleum (2 : 1)] to give the ketone as a mixture of two diastereoisomers. The less polar compound, the ketone (9) was obtained as a clear viscous oil (0.023 g, 31%) (R_f 0.61); $[\alpha]_D^{25}$ -9.7 (c = 1, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 1783 (C=O, β-lactam), 1721 (C=O, ketone) and 1644; δ_H (300 MHz, $CDCl_3$) 0.05 (3H, s, $SiCH_3$), 0.06 (3H, s, $SiCH_3$), 0.86 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.2, CH_3), 1.35 (1H, m, 5′-H), 1.64-1.80 (2H, m, 4′-H and 3′-H), 1.97 (1H, m, 4′-H), 2.15 (1H, m, 5′-H), 2.40 (1H, m, 3′-H), 2.75 (1H, ddd, $J_{3,NH}$ 0.8, $J_{3,4\ trans}$ 2.0, *J* 5.5, 3-H), 2.93 (1H, m, 6′-H), 3.65 (1H, dd, $J_{4,3\ trans}$ 2.0, $J_{4,6'trans}$ 10.0, 4-H), 4.15 (1H, m, CH_3CH), 4.70 (1H, ddd, *J* 2.0, *J* 4.5, $J_{H,F}$ 51.0, 2′-H), 6.08 (1H, br s, NH); δ_C (69.9 MHz, $CDCl_3$) -4.70 ($SiCH_3$), -4.38 ($SiCH_3$), 17.91 (SiC), 18.66 (4-CH_2, d, *J* 3), 22.89 (CH_3), 25.78 ($SiC(CH_3)_3$), 31.40 (5-CH_2), 33.76 (3-CH_2, *J* 25), 50.10 (3-CH), 52.40 (6′-CH), 63.68 (4-CH), 65.60 (CH_3CH), 92.68 (2′-CH, d, *J* 197), 167.60 (N-C=O), 207.89 (1′-C=O, d, *J* 24); δ_F (235.5 MHz, $CDCl_3$) -(26.96)-(-26.40) (CF, m).
LRMS (EI) : m/z 286 $[M-C(CH_3)_3]^+$ (100%), 268 $[M+H-C(CH_3)_3-F]^+$ (3%), 143 $[M-CH_3CH(OTBDMS)CHC=O]^+$ (11%), 75 $[(CH_3)_2SiOH]^+$ (100%). HRMS Found: $[M]^+$ 343.19866. $C_{16}H_{30}FNO_3Si$ requires M 343.19788.
The more polar isomer (R_f 0.44) was the ketone (8), isolated as a white solid (0.046 g, 62%), m.p. 110°C; $[\alpha]_D^{25}$ +1.2 (c = 1, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 3419 (NH), 1760 (β-lactam, C=O), 1730 (ketone, C=O); δ_H (300 MHz, $CDCl_3$) 0.04 (3H, s, $SiCH_3$), 0.05 (3H, s, $SiCH_3$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.2, CH_3), 1.55-1.65 (1H, m, 5′-H), 1.60 (3H, m, 4′-H_a 4′-H_e and 3′-H), 2.10 (1H, m, 5′-H), 2.34 (1H, m, 3′-H), 2.87 (1H, dd, $J_{3,4\ trans}$ 2.5, *J* 4.5, 3-H), 3.07 (1H, m, 6′-H), 3.95 (1H, d, $J_{4,3\ trans}$ 2.5, $J_{4,6'\ cis}$ 4.5, 4-H), 4.18 (1H, m, CH_3CH), 4.72 (1H, ddd, $J_{2',5'}$ 2.0, $J_{2',5'}$ 4.5, $J_{H,F}$ 51.0, 2′-H), 6.20 (1H, br s, NH); δ_C (75.5 MHz, $CDCl_3$) -5.01 ($SiCH_3$), -4.28 ($SiCH_3$), 17.92 (SiC), 18.68 (4′-CH_2, d, *J* 3), 22.49 ($CHCH_3$), 25.72 ($SiC(CH_3)_3$), 28.31 (5′-CH_2), 34.01 (3′-CH_2, d, *J* 22), 48.77 (3-CH), 49.59 (6′-CH, d, *J* 5.4), 61.17 (4-CH), 65.55 (CH_3CH), 93.10 (2′-CH, d, *J* 179), 168.55 (N-C=O), 207.86 (1′-C=O, d, *J* 22); δ_F (235.5 MHz, $CDCl_3$) (-27.16)-(-26.50) (CF, m). LRMS : m/z 286 $[M-C(CH_3)_3]^+$ (96%), 143 $[M-CH_3CH(OTBDMS)\ CHC=O]^+$ (14%).
HRMS Found: $[M]^+$ 343.19866. $C_{16}H_{30}FNO_3Si$ requires M 343.19788.

Allyl (4*S*, 8*S*, 9*R*, 10*S*, 12*R*)-4-fluoro-10-[(*S*)-1-(*tert*-butyldimethylsilyl-oxy)ethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (11). A solution of triethylamine (1.23 cm^3, 9.2 mmol) in xylene (20 cm^3) was cooled to 0°C. Allyl oxalyl chloride (0.655 cm^3, 6.9 mmol) was added to the solution. After 15 min the β-lactam (9) (0.792 g, 2.3 mmol) in xylene (7 cm^3) was added and the mixture was stirred at 0°C for 30 min. The mixture was washed with 1% aqueous sodium hydrogen carbonate (2 x 5 cm^3), water (5 cm^3), brine (5 cm^3) and dried ($MgSO_4$). The volume of the organic phase, containing the oxalimide (10), was then reduced under high vacuum to *ca* 10 cm^3 and triethyl phosphite (1.17 cm^3, 6.9 mmol) was added. The reaction mixture was heated to 140°C for 6 h. The reaction can be conveniently monitored by IR spectroscopy (disappearance of oxalimide C=O band at ~ 1810 cm^{-1}). The solvent was then evaporated under high vacuum and the oily residue purified by column chromatography [light petroleum (b.p. 40-60°C) / ethyl acetate (2 : 1)] to give the fluoro tribactam (11), obtained as a colourless oil (0.65 g, 67%) ν_{max} ($CHCl_3$)/cm^{-1} 1783 (β-lactam, C=O), 1721 (ketone, C=O) and 1664; δ_H (250 MHz, $CDCl_3$) 0.10 (6H, s, $Si(CH_3)_2$), 0.90 (9H, s, $SiC(CH_3)_3$), 1.20 (3H, d, *J* 6.20, CH_3), 1.25-2.00 (6H, m), 2.20 (1H, m), 3.20 (1H, dd, *J* 3.5, *J* 6.5, 10-H), 3.30 (1H, m, 8-H), 4.12-4.25 (2H, m, 9-H, 12-H), 4.73 (2H, 2 x dddd, ^4J 1.2, ^4J 1.5, $^3J_{vic}$ 5.5, $^2J_{gem}$ 11.0, -CH_2CHCH_2), 5.24 (1H, dddd, ^4J 1.2, ^4J 1.2, $^2J_{gem}$ 1.5, $^3J_{vic,cis}$ 10.5, -CH=CH_2), 5.40 (1H, dddd, $^2J_{gem}$ 1.5, ^4J 1.5, ^4J 1.5, $^3J_{vic,trans}$ 17.0, CH=CH_2), 5.93 (1H, dddd, $^3J_{vic}$ 5.5, $^3J_{vic}$ 5.5, $^3J_{vic,cis}$ 10.5, $^3J_{vic,trans}$ 17.0, CH_2CH=CH_2), 6.12 (1H, ddd, *J* 2.5, *J* 2.5, J_{HF} 51.0, 4-H); δ_C (75.5 MHz, $CDCH_3$) -5.00 ($SiCH_3$), -4.27 ($SiCH_3$), 17.88 (SiC), 20.08 (7-CH_2),

22.27 (CH_3), 25.69 ($SiC(CH_3)_3$), 30.25 (6-CH_2), 32.52 (5-CH_2, d, *J* 24), 44.32 (10-CH), 55.12 (8-CH), 61.34 (9-CH), 65.73 (CO_2CH_2), 66.15 (12-CH), 87.13 (4-CH, d, *J* 163), 118.44 ($CH=CH_2$), 126.17 (2-C, d, *J* 8), 131.28 ($CH=CH_2$), 144.23 (3-C, d, *J* 20), 160.26 (C=O, d, *J* 3), 175.57 (C=O, d, *J* 2).
LRMS (EI) : m/z 382 [M-CH_2=CH=CH_2] (10%), 366 [M-$C(CH_3)_3$]$^+$ (41%), 159 [M-CH_3CH(OTBDMS)]$^+$ (68%), 115 [TBDMS]$^+$ (59%), 73 [$SiC(CH_3)_3$]$^+$ (100%). HRMS (EI) Found: [M]$^+$ 423.22433. $C_{22}H_{34}FNO_4Si$ requires M 423.22411.

Allyl (4*S*,8*S*,9*R*,10*S*,12*R*)-4-fluoro-10-[(*S*)-1-hydroxyethyl]-11-oxo-1-aza tricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (12). Tribactam (**11**) (0.553 g, 1.3 mmol) was dissolved in THF (4 cm^3). Glacial acetic acid (1.07 cm^3, 13.7 mmol) and tetrabutylammonium fluoride (1M in THF) (15.4 cm^3, 15.4 mmol) were added and the mixture was heated to 30°C. After 2 h at 30°C, the mixture was diluted with ethyl acetate (50 cm^3), washed with ice-cold saturated ammonium chloride solution, 5% aqueous sodium hydrogen carbonate (15 cm^3), water (15 cm^3), brine (15 cm^3) and dried ($MgSO_4$). The solvent was evaporated under vacuum and the residue was purified by column chromatography [ethyl acetate / light petroleum (b.p. 40-60°C) (2 : 1)] to yield the alcohol (**12**) as a colourless oil (0.260 g, 65%) ν_{max} ($CHCl_3$)/cm^{-1} 3613 (OH), 1776 (β-lactam, C=O), 1726 (ester, C=O) and 1647 (C=C); δ_H (250 MHz, $CDCl_3$) 1.25 (3H, d, *J* 6.2, CH_3), 1.30-2.00 (6H, m), 2.25 (1H, m), 3.25 (1H, dd, *J* 3.5, *J* 6.5, 10-H), 3.40 (1H, m, 8-H), 4.20 (2H, m, 9-H, 12-H), 4.65-4.80 (2H, m, ^4J 1.2, ^4J 1.5, $^3J_{vic}$ 5.5), 5.28 (1H, dddd, ^4J 1.2, ^4J 1.2, $^2J_{gem}$ 1.5, $^3J_{vic,cis}$ 10.5, -CH_2CHCH_2), 5.44 (1H, dddd, J_{gem} 1.5, ^4J 1.5, ^4J 1.5, $J_{vic,trans}$ 17.0, -CH_2CHCH_2), 5.96 (1H, dddd, $^3J_{vic}$ 5.5, $^3J_{vic}$ 5.5, $^3J_{vic,cis}$ 10.5, $^3J_{vic,trans}$ 17.0, -CH_2CHCH_2), 6.15 (1H, ddd, *J* 2.0, *J* 3.5, $J_{H,F}$ 51.0, 4-H); δ_C (69.9 MHz, C_6D_6) 14.07 (CH_3), 20.32 (CH_2), 20.77, 21.65 (CH_3), 30.19 (CH_2), 32.57 (5-CH_2, d, *J* 28), 44.58 (8-CH), 55.39 (8-CH), 61.34 (9-CH), 63.62 (12-CH), 65.24 (CO_2CH_2), 84.45 (4-CH, d, *J* 181), 118.20 ($CH=CH_2$), 126.61 (2-C, d, *J* 8), 131.98 ($CH_2=CH$), 144.00 (3-C, d, *J* 19), 160.65 (O-C=O), 175.57 (N-C=O). LRMS (EI) : m/z 265 [M+H-CH_3CH(OH)]$^+$ (6%), 224 [M+H-CH_3CH(OH)CHC=O]$^+$ (10%), 204 [M-CH_3CH(OH)CHC=O-F]$^+$ (19%), 84 [$CO_2CH_2CH=CH_2$+H]$^+$ (100%). HRMS (EI) Found: [M]$^+$ 309.13793. $C_{16}H_{20}FNO_4$ requires M 309.13763.

Sodium (4*S*, 8*S*, 9*R*, 10*S*, 12*R*)-4-fluoro-10-[(*S*)-1-hydroxyethyl]-11-oxo-1-azatricyclo[7.2.0.0^{3,8}]-undec-2-ene-2-carboxylate (13). A mixture of $Pd(PPh_3)_4$ (14 mg, 0.04 eq) and triphenylphosphine (2.4 mg, 0.03 eq) in THF (0.5 cm^3) was added to a solution of the alcohol (**12**) (100 mg, 0.323 mmol) in THF (1.5 cm^3). After 5 min sodium-2-ethylhexanoate (45 mg, 1 eq.) in THF (0.5 cm^3) was added. A white solid precipitated out of solution. After 1 h the volume of the reaction mixture was reduced under vacuum to *ca* 1 cm^3 and diethyl ether (~ 2 cm^3) was added. The solution was centrifuged and the supernatant decanted. The solid was washed with diethyl ether / THF mixture (9 : 1) (3 x 3 cm^3) and dried under high vacuum. The sodium salt (**13**) was obtained as a white powder (84 mg, 90%) ν_{max} (KBr)/cm^{-1} 3400 (OH), 1771 (C=O), 1730, 1617 and 1587; δ_H (300 MHz, d^{6}DMSO) 1.12 (3H, d, $J_{13,12}$ 6.2, CH_3), 1.24 (1H, m, 7-H), 1.45 (1H, m, 5-H), 1.61-1.78 (3H, m, 6-H_a, 6-H_e and 7-H), 1.90-2.08 (1H, m, 5-H), 2.95-3.04 (1H, m, 8-H), 3.07 (1H, dd, $J_{10,9\ trans}$ 3, $J_{10,12\ trans}$ 6.5, 10-H), 3.91 (1H, m, $J_{12,OH}$ 4.5, $J_{12,13}$ 6.2, $J_{12,10\ trans}$ 6.5, 12-H), 3.96 (1H, dd, $J_{9,10\ trans}$ 3.0, $J_{9,8\ cis}$ 10.0, 9-H), 4.93 (1H, d, $J_{OH,12}$ 4.5, OH) 6.34 (1H, dt, *J* 2.5, $J_{H,F}$ 51.0, 4-H). LRMS (EI) : m/z 205 [M-CH_3CH(OH)CHC=O]$^+$ (1%), 187 [M+H-CH_3CH(OH)CHC=O-F]$^+$ (10%). HRMS (EI) Found: [M]$^+$ 291.09323. $C_{13}H_{15}FNNaO_4$ requires M 291.08831.

Imino-Acid (14). NMR spectra were recorded over a period of time on a solution of the tribactam (**13**) in D_2O and showed complete conversion to compound (**14**) after 18 hours. δ_H (500 MHz, D_2O) 1.06 (3H, d, *J* 6.5), 1.42 (1H, m), 1.58 (1H, m), 1.87 (2H, m), 2.19 (1H, m), 2.27 (1H, dd, *J* 1.9, 6.5), 2.28 (1H, m), 3.10 (1H, m), 3.80 (1H, m), 4.71 (1H, dd, *J* 1.9, 9.7), 7.02 (1H, m).

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A Highly Diastereoselective Synthesis of *Trans*-3,4-(Difluoromethano)glutamic Acid

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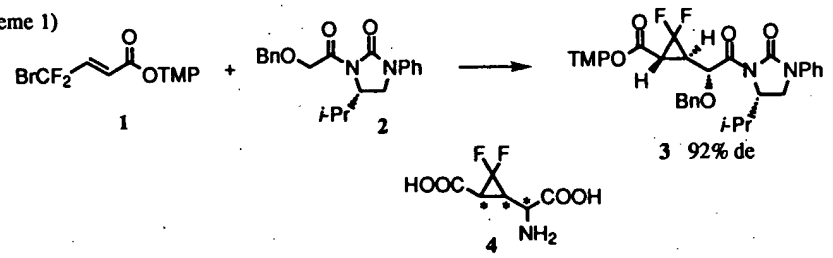
Abstract: Reaction of enantiomerically pure *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** with lithium enolate of *N*-diphenylmethylideneglycinate **6** in DMF proceeded in highly diastereoselective manner to give *trans*-disubstituted *gem*-difluorocyclopropane **7**, which was readily converted to the 3,4-(difluoro- methano)glutamic acid **4**.

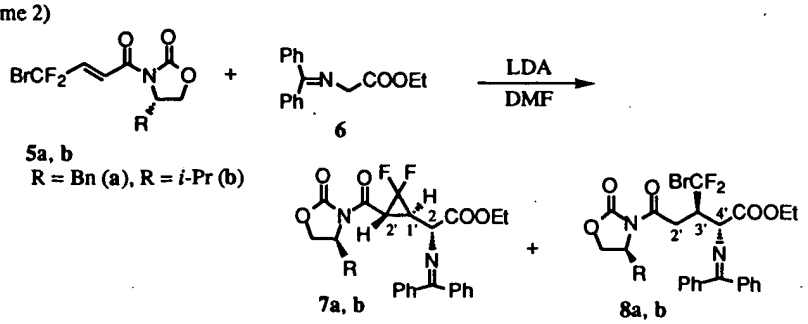
Introduction of cyclopropane moiety into biologically active substances has been recognized as one of the important chemical modifications owing to conformational rigidity and potential chemical reactivity brought about by this modification.[1-4] For example, conformationally restricted analogs of glutamic acid having the cyclopropane moiety were studied so as to elucidate the importance of conformations (extended and folded forms) for the receptor subtype specificity.[5] For such chemically modified substances, the introduction of fluorine atom(s) onto the cyclopropane ring would lead to interesting results in consideration of characteristic features of fluorinated compounds.[6] We have reported a regio- and stereoselective preparation of functionalized *gem*-difluorocyclopropanes through the sequential Michael addition of lithium enolate of ester or amide to 2,4,6-trimethylphenyl (TMP) 4-bromo-4,4-difluorocrotonate **1** followed by the triethylborane mediated intramolecular substitution reaction.[7] Furthermore, we have extended this reaction in asymmetric version using *N*-acylimidazolidinone derivative **2** as a Michael donor (Scheme 1).[8] For the synthesis of 3,4-(difluoromethano)glutamic acid **4**, attempts were made to conduct the reaction of **1** with several glycine derivatives having chiral auxiliary in ester part, but we could not obtain satisfactory results with respect to chemical yield and diastereoselectivity.

(Scheme 1)



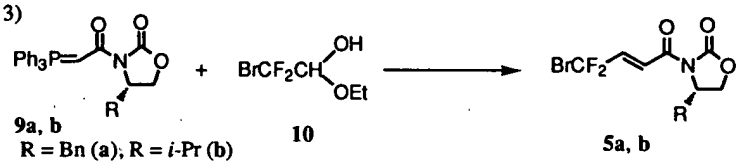
As an alternative approach, we introduced a chiral auxiliary into Michael acceptor. In this paper, we report that *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** serves as an efficient starting material for a highly diastereoselective preparation of *trans*-3,4-(difluoromethano)glutamic acid **4** through the reaction of **5** with *N*-(diphenylmethylidene)glycinate **6** (Scheme 2).

(Scheme 2)



The *N*-crotonoyloxazolidinones **5a,b** was obtained exclusively in *E* form by the Wittig reaction of the phosphoranes **9a,b** with bromodifluoroacetaldehyde hemiacetal **10**, prepared by DIBAL-H reduction of ethyl bromodifluoroacetate (Scheme 3).[7,9]

(Scheme 3)



For the synthesis of the (difluoromethano)glutamate derivative **7a**, reaction of **5a** with lithium enolate of ethyl *N*-(diphenylmethylidene)glycinate **6**[10] was conducted under several reaction conditions. Results are summarized in Table 1. In THF, reaction of **5a** with lithium enolate of **6** proceeded at low temperature (-78 °C) to give the 1,4-addition product **8a** in excellent yield with a high diastereoselectivity (entry 1), but no cyclopropane formation was observed by extending the reaction time at room temperature. Under similar reaction conditions for the synthesis of the difluorocyclopropane **3** from **1** and **2** as reported previously,[7,8] we obtained the desired cyclopropane **7a** in low yield (16%) along with **8a** as a major product (entry 2). When HMPA was added as co-solvent, chemical yield of **7a** increased to 43% and the diastereoselectivity of **7a** thus obained was found 71% de (entry 3). Finally, **7a** was obtained in highly diastereoselective manner when the reaction was carried out in DMF and no appreciable effect of triethylborane as an additive was observed (entries 4, 5). It is worth to note that the major isomers of both **7a** and **8a** thus obtained in each experiment were identical. The absolute stereochemistry of the cyclopropane **7a** was confirmed to be 2*R*,1'*R*,2'*R* as described later. Similar results (chemical yield, diastereoselectivity and the sense of asymmetric induction) were obtained in the reaction of **6** with **5b** instead of **5a**.

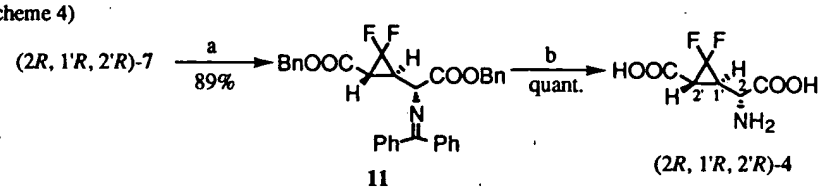
Table 1. Reactions of **5a** with **6**

entry	Solvent	Additive	Cyclopropane **7a** Yield(%)[a] [% de][b]	1,4-Adduct **8a** Yield(%)[a] [% de][b]
1	THF	—	0	93 [>95]
2	THF	Et_3B, DMI[c]	16 —[d]	84 —[d]
3	THF	HMPA[e]	43 [71]	48 [>95]
4	DMF	—	54 [>95]	16 [>95]
5	DMF	Et_3B[f]	47 [>95]	12 [>95]

a) Isolated yield. b) Determined by ^{19}F-NMR spectrum of reaction mixture. When a minor isomer could not be detected by ^{19}F-NMR, de was shown as >95%. c) DMI = 1,3-Dimethyl-2-imidazolidinone. d) Not determined. e) THF : HMPA = 10 : 1. f) 3 eq. Et_3B was added.

Conversion of (2*R*,1'*R*,2'*R*)-**7a** to the 3,4-(difluoromethano)glutamic acid **4** [2-(2'-carboxy-3',3'-difluoro)cyclopropylglycine] was readily achieved by titanium isopropoxide catalyzed ester exchange reaction with excess of benzyl alcohol[11] followed by hydrogenolysis, as shown in Scheme 4.

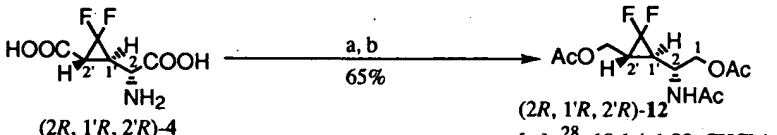
(Scheme 4)



a) BnOH, Ti(O*i*Pr)$_4$, 80°C b) H_2/Pd-C, EtOH

Determination of the stereochemistry of 3,4-(difluoromethano)glutamic acid **4** was carried out by comparison of $[\alpha]_D$ value, and ^{1}H-, ^{13}C- and ^{19}F-NMR spectra of the triacetyl derivative **12** formed from **4** with those data of the two authentic diastereomers prepared from the known precursors **14**.[8] Thus, borane reduction of **4** and subsequent reaction with Ac_2O in pyridine gave the triacetyl derivative **12** in 65% yield (Scheme 5). For the synthesis of authentic samples [(2*R*,1'*R*,2'*R*)- and (2*R*,1'*S*,2'*S*)-**12**], each diastereomer of the difluorocyclopropane **14**, which were prepared by difluorocarbene addition to the allylic alcohol derivative **13** and their stereochemistries were confirmed on the basis of X-ray crystallographic analysis[8] was

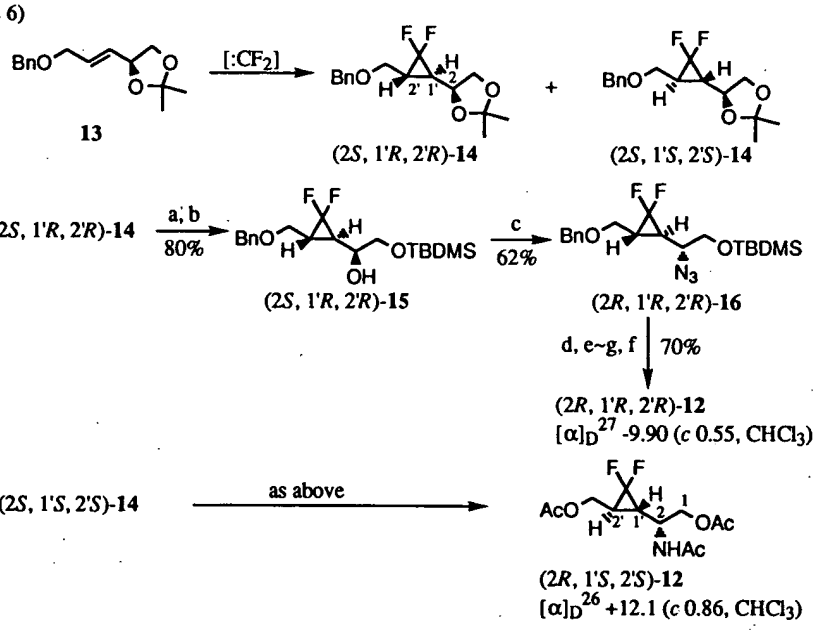
(Scheme 5)



$[\alpha]_D^{28}$ -10.1 (*c* 1.00, $CHCl_3$)

a) BH_3•DMS, THF b) Ac_2O, pyridine

(Scheme 6)



$[\alpha]_D^{27}$ -9.90 (*c* 0.55, $CHCl_3$)

$[\alpha]_D^{26}$ +12.1 (*c* 0.86, $CHCl_3$)

a) 10% HCl, MeOH; b) TBDMS-Cl, imidazole, DMF; c) Ph_3P, DEAD, $(PhO)_2P(O)N_3$; d) TBAF, THF; e) H_2/Pd-C, AcOEt; f) Ac_2O, pyridine; g) H_2/$Pd(OH)_2$, AcOEt

used as a precursor (Scheme 6). Substitution of the secondary hydroxyl group of **15** by azide group with inversion by Mitsunobu reaction[12] followed by the ordinary reactions (desilylation, reduction of azide group, acetylation, debenzylation and acetylation) provided the corresponding triacetyl derivatives **12** having 2*R*,1'*R*,2'*R* and 2*R*,1'*S*,2'*S* configurations, respectively. Fortunately, physical data of (2*R*,1'*R*,2'*R*)-**12**, prepared from **13**, were identical with those of **12** derived from 3,4-(difluoromethano)glutamic acid **4**, thereby the absolute configuration of **4** was confirmed to be 2*R*,1'*R*,2'*R*.[13] This indicates that conjugate addition of lithium enolate of **6** proceeded in a manner of C(β)-*re*-face preference with respect to the Michael acceptor **5**, while the transition state of the conjugate addition was not clear because we could not determine the stereochemistry of the Michael donor, lithium enolate of **6** in DMF.

In summary, we have shown that *N*-(4'-bromo-4',4'-difluorocrotonoyl)oxazolidinone **5** is an efficient starting material for the asymmetric preparation of functionalized *trans*-disubstituted *gem*-difluorocyclopropanes, including glutamic acid derivative **4**. We are currently carring out synthesis of other isomers of **4**.

EXPERIMENTAL

^{1}H- and ^{13}C-NMR spectra were taken on a Brucker AM400 or a Varian Gemini-300 spectrometer, and chemical shifts were reported in parts per million (ppm) using $CHCl_3$ (7.26 ppm) in $CDCl_3$ or sodium 3-(trimethylsilyl)propionate-2,2,3,3-d_4 (TSP) (0 ppm) in D_2O for ^{1}H-NMR, and $CDCl_3$ (77.01 ppm) in $CDCl_3$ or TSP (0 ppm) in D_2O for ^{13}C-NMR as an internal standard, respectively. ^{19}F-NMR spectra were taken on a Brucker AM400 spectrometer and chemical shifts were reported in ppm using benzotrifluoride (0 ppm) as a standard. Infrared spectra (IR) were recorded on a Perkin-Elmer FTIR-1710 infrared spectrophotometer. Mass spectra (MS) were obtained on a Hitachi M-80 or VG Auto spec. Specific rotations were recorded on a JASCO DIP spectrometer. Medium pressure liquid chromatography (MPLC) was performed using prepacked column (silica gel, 50 μm) with UV detector.

(4*S*)-3-[(*E*)-4'-Bromo-4',4'-difluoro-2'-butenoyl]-4-benzyl-2-oxazolidinone (5a). Under Ar atmosphere, a solution of (4*S*)-*N*-bromoacetyl-4-benzyl-2-oxazolidinone (3.7 g, 12.4 mmol) and triphenylphosphine (3.6 g, 13.7 mmol) in CH_3CN (15 mL) was stirred for 2 days at 50 °C. To the reaction mixture was added 2*N* NaOH aq.(6.5 mL) and it was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure to leave the crude phosphorane **9a**. A mixture of ethyl bromodifluoroacetate (1.7 mL, 13.7 mmol) and DIBAL-H (0.93 *M* in hexane, 14.7 mL, 13.7 mmol) in Et_2O (10 mL) was stirred for 20 min at -78 °C. To the reaction mixture was added MeOH (5 mL), then 5% HCl (10 mL) and the whole was stirred for 10 min at room temperature. The mixture was extracted with Et_2O and the organic layer was successively washed with sat. $NaHCO_3$ aq. and brine, dried over $MgSO_4$ then concentrated under reduced pressure. A solution of the residue and the crude phosphorane **9a** described above in THF (35 mL) was stirred for 5 h at room temperature. Removal of solvent under reduced pressure to leave the residue, which was purified by silica gel column chromatography (hexane- AcOEt =10 : 1-5 : 1) to give **5a** (2.88 g, 65%). Colorless oil. $[\alpha]_D^{26.4}$ +59.2 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3064, 2923, 1786, 1691. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.81 (1 H, dd, *J* = 13.5, 9.6 Hz), 3.35 (1 H, dd, *J* = 13.5, 3.4 Hz), 4.15-4.35 (2 H, m), 4.75 (1 H, dddd, *J* = 9.6, 7.0, 3.4, 3.4 Hz), 7.14 (1 H, dt, *J* = 15.3, 10.2 Hz), 7.20-7.45 (5 H, m), 7.74 (1 H, dt, *J* = 15.3, 1.8 Hz). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 37.6, 55.3, 66.5, 115.4 (t, *J* = 301.5 Hz), 122.9 (t, *J* = 6.4 Hz), 127.5, 129.1, 129.4, 134.8, 139.1 (t, *J* = 25.8 Hz), 153.0, 162.6. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 13.4 (dd, *J* = 10.2, 1.6 Hz). MS (EI) m/z; 360, 358 (M^+), 230, 183, 91. Anal. Calcd for $C_{14}H_{12}BrF_2NO_3$: C, 46.69; H, 3.36; N, 3.89. Found: C, 47.05; H, 3.39; N, 3.91.

(4*S*)-3-[(*E*)-4'-Bromo-4',4'-difluoro-2'-butenoyl]-4-isopropyl-2-oxazolidinone (5b). In a similar procedure for the preparation of **5a**, **5b** was obtained in 56% yield. Colorless prisms. mp 59.5 - 62.5 °C. $[\alpha]_D^{22.4}$ +77.6 (*c* 1.00, $CHCl_3$). IR (KBr) ν, cm^{-1}; 1775, 1679, 1391, 1371, 1342, 1210. ^{1}H-NMR (300 MHz, $CDCl_3$) δ; 0.90 (3 H, d, *J* = 7.0 Hz), 0.95 (3 H, d, *J* = 7.0 Hz), 2.42 (1 H, dtt, *J* = 7.0, 6.9, 4.0 Hz), 4.27 (1 H, dd, *J* = 9.2, 3.3 Hz), 4.33 (1 H, dd, *J* = 9.2, 8.0 Hz), 4.50 (1 H, ddd, *J* = 8.1, 4.0,

3.5 Hz), 7.08 (1 H, dt, J = 15.4, 10.2 Hz), 7.75 (1 H, dt, J = 15.2, 1.7 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ; 14.6, 17.9, 28.3, 58.7, 63.7, 115.3 (t, J = 302.0 Hz), 122.9 (t, J = 6.7 Hz), 138.8 (t, J = 25.6 Hz), 153.5, 162.4. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 13.6 (dd, J = 10.3, 1.5 Hz). Anal. Calcd for $C_{10}H_{12}BrF_2NO_3$: C, 37.29; H, 3.75; N, 4.35. Found: C, 37.44; H, 3.91; N, 4.51.

(2*R*,1'*R*,2'*R*,4"*S*)-Ethyl *N*-diphenylmethylidene-2-[2'-{(4"-benzyl-2"-oxazolidinon-3"-yl)carb nyl}-3',3'-diflu ro]cyclopropylglycinate (7a) and (4*S*,3'*R*,4'*R*)-3-[3'-br mo-difluoromethyl-4'-(diphenylmethylideneamino)-4'-ethoxycarbonyl]butanoyl-4-benzyl-2-oxazolidinone (8a). Experimental procedure corresponding to entry 4 in Table 1 is shown. Under Ar atmosphere, a mixture of the glycinate **6** (756 mg, 2.83 mmol) and LDA, formed from *N*,*N*-diisopropylamine (0.47 mL, 3.34 mmol) and *n*-butyllithium (1.65 *M* in hexane, 1.87 mL), in DMF (15 mL) was stirred for 15 min at -20 °C, and to this was added **5a** (926 mg, 2.57 mmol) in DMF (10 mL). After being stirred for 2 h at the same temperature and then quenched by addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=7:1) to give **7a** (758 mg, 54%) and **8a** (245 mg, 16%), respectively. **7a**; colorless oil. $[\alpha]_D^{26.0}$ +39.4 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3063, 1782, 1739, 1700, 701. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.30 (3 H, t, J = 7.1 Hz), 2.84 (1 H, dd, J = 13.5, 9.3 Hz), 3.25 (1 H, dd, J = 13.5, 3.2 Hz), 3.31 (1 H, m), 3.85 (1 H, dd, J = 14.1, 7.8 Hz), 4.13 (1 H, d, J = 8.1 Hz), 4.15-4.35 (4 H, m), 4.71 (1 H, m), 7.18-7.65 (15 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.0, 29.3 (dd, J = 11.0, 10.6 Hz), 30.9 (dd, J = 8.8, 7.8 Hz), 37.6, 55.4, 61.3, 61.8, 66.2, 111.7 (dd, J = 293.2, 290.2 Hz), 127.4, 127.7, 128.1, 128.7, 128.97, 129.02, 129.04, 129.4, 130.8, 134.8, 135.5, 139.0, 153.3, 164.5, 169.2, 172.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -71.6 (1 F, dd, J = 152.7, 13.9 Hz), -69.2 (1 F, dd, J = 152.7, 14.0 Hz). MS (EI) m/z; 546 (M^+), 473, 296, 182, 105. Anal. Calcd for $C_{31}H_{28}F_2N_2O_5$: C, 68.12; H, 5.16; N, 5.13. Found: C, 68.31; H, 5.16; N, 5.10. **8a**; colorless oil. $[\alpha]_D^{26.8}$ -3.78 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3062, 1782, 1740, 1703, 701. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.27 (3 H, t, J = 7.1 Hz), 2.76 (1 H, dd, J = 13.4, 9.6 Hz), 3.24 (1 H, dd, J = 18.1, 3.9 Hz), 3.29 (1 H, dd, J = 13.4, 3.2 Hz), 3.82 (1 H, dd, J = 8.4, 8.4 Hz), 4.01 (1 H, dd, J = 18.1, 7.8 Hz), 4.06 (1 H, dd, J = 9.0, 2.6 Hz), 4.16-4.21 (3 H, m), 4.53 (1 H, d, J = 4.1 Hz), 4.64 (1 H, m), 7.19-7.63 (15 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 14.0, 32.7, 37.7, 50.0 (dd, J = 19.6, 19.5 Hz), 55.3, 61.6, 63.6, 66.1, 124.4 (dd, J = 309.0, 308.6 Hz), 127.3, 127.7, 128.0, 128.5, 128.9, 129.0, 129.3, 130.7, 135.3, 135.7, 139.1, 153.3, 169.6, 170.0, 172.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; 15.5 (1 F, dd, J = 161.0, 11.9 Hz), 16.0 (1 F, dd, J = 161.0, 11.4 Hz). MS (EI) m/z; 626 (M^+-1), 553, 497, 266, 193, 165. Anal. Calcd for $C_{31}H_{29}BrF_2N_2O_5$: C, 59.34; H, 4.66; N, 4.46. Found: C, 59.34; H, 4.71; N, 4.38.

(2*R*,1'*R*,2'*R*)-2-(2'-Carboxy-3',3'-difluoro)cyclopropylglycine (4). A mixture of benzyl alcohol (1 mL) and Ti(O*i*-Pr)$_4$ (154 mg, 0.54 mmol) was stirred for 30 min at room temperature under reduced pressure (4 mmHg). To the residue was added **7a** (100 mg, 0.18 mmol) and the mixture was stirred for 7 h at 70 °C. Purification of the mixture by silica gel column chromatography (hexane-AcOEt=10:1) gave the dibenzyl ester **11** (87 mg, 89%). Colorless oil. $[\alpha]_D^{25.6}$ -21.0 (*c* 1.00, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 2.40 (1 H, dd, J = 11.4, 7.6 Hz), 3.09 (1 H, dddd, J = 12.3, 7.6, 7.4, 3.5 Hz), 4.18 (1 H, d, J = 7.2 Hz), 5.181 (1 H, d, J = 12.4 Hz), 5.184 (2 H, s), 5.18 (2 H, s), 5.23 (1 H, d, J = 12.4 Hz), 7.10-7.61 (20 H, m). ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -70.7 (1 F, dd, J = 156.9, 12.5 Hz), -70.1 (1 F, ddd, J = 157.1, 11.8, 3.1 Hz). Under hydrogen atmosphere, a mixture of **11** (87 mg, 0.16 mmol) and 5% Pd-C in MeOH (1 mL) was stirred for 5 h at room temperature. After removal of catalyst by filtration, the filtrate was partitioned by hexane and water. The aqueous layer was concentrated under reduced pressure to leave solid mass, which was washed with Et_2O to give **4** (31 mg, quant.). Colorless prisms. 200 °C dec. $[\alpha]_D^{23.2}$ +39.4 (*c* 1.00, H_2O). IR (KBr) ν, cm^{-1}; 3106, 1621, 1530, 1476, 1393. ^{1}H-NMR (400 MHz, D_2O) δ; 4.16 (1 H, m), 4.25 (1 H, dd, J = 15.0, 7.8 Hz), 3.70 (1 H, d, J = 10.7 Hz). ^{13}C-NMR (100.6 MHz, D_2O) δ; 31.3 (dd, J = 11.6, 8.6 Hz), 34.1 (br), 54.2 (br), 113.7 (dd, J = 288.2, 286.1 Hz), 172.7, 173.7. ^{19}F-NMR

(376.5 MHz, D_2O) δ; -71.4 (1 F, dd, *J* = 157.6, 13.6 Hz), -69.0 (1 F, dd, *J* = 157.2, 14.8 Hz). MS(ESI) m/z; 195.9.

(2*R*,1'*R*,2'*R*)-2-Acetylamin -2-(2'-acetoxymethyl-3',3'-diflu ro)cyclopr pylethyl acetate (12). Under Ar atmosphere, a mixture of **(2*R*,1'*R*,2'*R*)-4** (20 mg, 0.1 mmol) and BH_3•DMS (10 *M* in THF, 0.4 mmol) in THF (1 mL) was stirred for 6 h at room temperature. After addition of MeOH (1 mL), the reaction mixture was concentrated under reduced pressure (4 mmHg) overnight. The residue was treated with acetic anhydride (33 μL, 0.35 mmol) in pyridine (1 mL) for 5 h at 0 °C, and then the reaction mixture was concentrated under reduced pressure after addition of MeOH (1 mL). The residue was chromatographed on silica gel (hexane-AcOEt=1:1) to give **12** (19 mg, 65%). Colorless prisms. mp 132.5-135.5 °C. $[\alpha]_D^{27.6}$ -10.1 (*c* 1.00, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3290, 1735, 1651, 1552. ^{1}H-NMR (300 MHz, $CDCl_3$) δ; 1.67 (1 H, dddd, *J* = 10.2, 10.2, 6.9, 4.3 Hz), 1.99 (3 H, s), 2.04 (1 H, m), 2.07 (3 H, s), 2.11 (3 H, s), 4.05 (1 H, dddd, *J* = 9.3, 9.3, 9.3, 4.1 Hz), 4.11 (2 H, d, *J* = 7.8 Hz), 4.13 (1 H, dd, *J* = 11.3, 4.6 Hz), 4.23 (1 H, dd, *J* = 11.3, 5.2 Hz), 5.79 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.7, 20.8, 23.2, 26.6 (dd, *J* = 10.8, 10.2 Hz), 29.5 (dd, *J* = 10.4, 9.6 Hz), 46.9, 60.7, 65.3, 113.2 (dd, *J* = 286.7, 286.7 Hz), 169.7, 170.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.8 (1 F, ddd, *J* = 163.8, 10.3, 2.3 Hz), -74.3 (1 F, ddd, *J* = 166.2, 10.6, 3.2 Hz). MS (EI) m/z; 294 (M^+), 178, 116, 84. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.69; H, 5.72; N, 4.78.

(2*S*,1'*R*,2'*R*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-hydroxyethyl *tert*-butyldimethylsilyl ether (15-Minor). **(2*S*,1'*R*,2'*R*)-14** (237 mg, 0.92 mmol) obtained as a minor isomer of difluorocarbene addition with **13**[8] was treated with 10% HCl in MeOH (2 mL) for 6 h at room temperature. After concentrated under reduced pressure, the residue was extracted with AcOEt by addition of sat. $NaHCO_3$ aq. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was treated with imidazole (138 mg, 2 mmol) and TBDMS-Cl (167 mg, 1.1 mmol) in DMF (2 mL) for 5 h at room temperature. After addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=15:1) to give **15-Minor** (273 mg, 79%). Colorless oil. $[\alpha]_D^{25.6}$ +15.5 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3454, 2954, 2930, 1114, 838. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.077 (6 H, s), 0.90 (9 H, s), 1.55 (1 H, m), 1.74 (1 H, dddd, *J* = 14.4, 7.3, 7.2, 7.1 Hz), 2.49 (1 H, d, *J* = 5.2 Hz), 3.51-3.56 (2 H, m), 3.61 (1 H, dd, *J* = 10.0, 6.0 Hz), 3.75 (1 H, dd, *J* = 10.0, 3.4 Hz), 4.48 (1 H, d, *J* = 12.0 Hz), 4.56 (1 H, d, *J* = 12.0 Hz), 7.29-7.37 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.51, 18.2, 25.7 (dd, *J* = 10.8, 10.8 Hz), 25.8, 28.9 (dd, *J* = 10.5, 10.4 Hz), 65.7, 65.87, 65.9, 69.7, 69.72, 72.5, 114.1 (dd, *J* = 286.2, 286.2 Hz), 127.5, 127.7, 128.4, 137.9. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.7 (1 F, dd, *J* = 163.1, 13.1 Hz), -74.9 (1 F, dd, *J* = 163.0, 13.1 Hz). MS (EI) m/z; 297, 193, 147, 91. Anal. Calcd for $C_{19}H_{30}F_2O_3Si$: C, 61.26; H, 8.12. Found: C, 61.27; H, 8.18.

(2*R*,1'*R*,2'*R*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-azidoethyl *tert*-butyldimethylsilyl ether (16-Minor). A mixture of **15-Minor** (222 mg, 0.6 mmol), triphenylphosphine (262 mg, 1.0 mmol), diphenylphosphoryl azide (0.19 mL, 0.9 mmol) and diethyl azodicarboxylate (0.14 mL, 0.9 mmol) in THF (4 mL) was stirred for 6 h at room temperature. After addition of sat. NH_4Cl aq., the reaction mixture was extracted with Et_2O. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane-AcOEt=20:1-10:1) to give **16-Minor** (243 mg, 98%). Colorless oil. $[\alpha]_D^{25.6}$ +37.1 (*c* 0.99, $CHCl_3$). IR (neat) ν, cm^{-1}; 2955, 2931, 1256, 1115, 839. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.10 (6 H, s), 0.92 (9 H, s), 1.63 (1 H, dddd, *J* = 11.8, 9.9, 7.1, 2.4 Hz), 1.93 (1 H, m), 3.18 (1 H, ddd, *J* = 9.3, 4.5, 4.4 Hz), 3.53 (1 H, dd, *J* = 10.8, 8.1 Hz), 3.66 (1 H, m), 3.73 (1 H, dd, *J* = 10.5, 5.9 Hz), 3.83 (1 H, dd, *J* = 10.5, 3.8 Hz), 4.53 (1 H, d, *J* = 12.0 Hz), 4.56 (1 H, d, *J* = 11.9 Hz), 7.28-7.36 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.64, -5.70, 18.2, 25.7, 26.4 (dd, *J* = 10.2, 10.2 Hz), 27.3 (dd, *J* =

10.2, 10.1 Hz), 60.6, 65.6, 66.0, 72.5, 113.5 (dd, J = 287.6, 287.4 Hz), 127.6, 127.7, 128.4, 137.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.5 (1 F, dd, J = 162.7, 11.6 Hz), -74.0 (1 F, dd, J = 162.9, 11.6 Hz). MS (EI) m/z; 267, 224, 148, 115, 91. Anal. Calcd for $C_{19}H_{29}F_2N_3O_2Si$: C, 57.41; H, 7.35; N, 10.57. Found: C, 57.67; H, 7.41; N, 10.21.

(2*R*,1'*R*,2'*R*)-2-Acetylamin -2-(2'-acet xymethyl-3',3'-difluor)cycl pr pylethyl acetate (12-Minor). After deprotection of TBDMS group by treating **16-Minor** (37 mg, 0.064 mmol) with TBAF (1*M* in THF, 0.3 mL) in THF for 3 h at room temperature and subsequent purification by silica gel column chromatography (hexane-AcOEt=15:1-8:1), a mixture of the desilylated azide derivative (18 mg) and 5% Pd-C in AcOEt (1 mL) was stirred for 24 h under hydrogen atmosphere. Removal of the catalyst by filtration and evaporation of the filtrate gave the residue, which was treated with acetic anhydride in pyridine for 5 h at room temperature. The reaction mixture was concentrated under reduced pressure and the residue was hydrogenated over $Pd(OH)_2$ for 5 h at room temperature for debenzylation. The crude product was acetylated by repeating the similar procedure as above to give **12-Minor** (13 mg, 69%). Colorless prisms. mp 132.8-134.5 °C. $[\alpha]_D^{26.8}$ -9.90 (*c* 0.55, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3292, 1736, 1652, 1553. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.67 (1 H, dddd, J = 10.6, 10.5, 7.0, 4.0 Hz), 1.99 (3 H, s), 2.04 (1 H, m), 2.07 (3 H, s), 2.11 (3 H, s), 4.05 (1 H, dddd, J = 9.5, 9.5, 9.3, 4.6 Hz), 4.11 (2 H, d, J = 6.5 Hz), 4.13 (1 H, dd, J = 11.5, 4.6 Hz), 4.23 (1 H, dd, J = 11.3, 5.3 Hz), 5.79 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.67, 20.7, 23.1, 26.4 (dd, J = 9.9, 9.9 Hz), 29.4 (dd, J = 10.4, 10.1 Hz), 46.8, 60.7, 65.2, 113.2 (dd, J = 288.0, 287.7 Hz), 169.8, 170.8. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.8 (1 F, ddd, J = 165.3, 10.3, 2.2 Hz), -74.3 (1 F, ddd, J = 165.6, 10.5, 3.2 Hz). MS (EI) m/z; 294 (M^+), 178, 116, 84. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.16; H, 5.71; N, 4.78.

(2*S*,1'*S*,2'*S*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-hydroxyethyl *tert*-butyldimethylsilyl ether (15-Major). Colorless oil. $[\alpha]_D^{28.4}$ -10.6 (*c* 1.00, $CHCl_3$). IR (neat) ν, cm^{-1}; 3424, 2954, 2931, 1255. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.092 (6 H, s), 0.91 (9 H, s), 1.52 (1 H, ddd, J = 15.6, 7.5, 7.5 Hz), 1.97 (1 H, ddd, J = 14.9, 14.4, 7.3 Hz), 2.35-2.60 (1 H, br), 3.52 (2 H, m), 3.57 (1 H, dd, J = 9.8, 6.3 Hz), 3.68 (1 H, dddd, J = 10.9, 6.5, 2.1, 2.1 Hz), 3.73 (1 H, dd, J = 9.8, 3.3 Hz), 4.53 (1 H, d, J = 11.9 Hz), 4.60 (1 H, d, J = 11.9 Hz), 7.26-7.35 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.45, 18.3, 25.8, 26.7 (dd, J = 10.3, 10.0 Hz), 29.0 (dd, J = 9.6, 9.5 Hz), 65.9, 66.6, 69.4, 72.4, 113.9 (dd, J = 287.0, 287.0 Hz), 127.7, 128.4, 137.9. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -74.0 (dd, J = 7.6, 7.2 Hz). MS (EI) m/z; 297, 193, 147, 91. Anal. Calcd for $C_{19}H_{30}F_2O_3Si$: C, 61.26; H, 8.12. Found: C, 61.33; H, 8.18.

(2*R*,1'*S*,2'*S*)-2-(2'-Benzyloxymethyl-3',3'-difluoro)cyclopropyl-2-azidoethyl *tert*-butyldimethylsilyl ether (16-Major). Colorless oil. $[\alpha]_D^{26.8}$ -3.03 (*c* 0.99, $CHCl_3$). IR (neat) ν, cm^{-1}; 2931, 2109, 1255, 1115, 839. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 0.085 (6 H, s), 0.91 (9 H, s), 1.63 (1 H, ddd, J = 13.0, 10.1, 7.0 Hz), 1.78 (1 H, dddd, J = 13.7, 7.1, 7.1, 7.1 Hz), 3.21 (1 H, dddd, J = 10.0, 6.1, 3.7, 1.4 Hz), 3.56 (2 H, d, J = 7.0 Hz), 3.71 (1 H, dd, J = 10.6, 6.1 Hz), 3.81 (1 H, dd, J = 10.6, 3.7 Hz), 4.49 (1 H, d, J = 12.0 Hz), 4.65 (1 H, d, J = 12.0 Hz), 7.26-7.37 (5 H, m). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; -5.62, 18.2, 25.7, 26.8 (dd, J = 11.0, 10.8 Hz), 27.3 (dd, J = 10.7, 10.6 Hz), 61.3, 65.0, 65.6, 65.63, 72.7, 113.5 (dd, J = 287.1, 287.0 Hz), 127.5, 127.7, 128.4, 137.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.5 (1 F, dd, J = 163.3, 13.0 Hz), -74.2 (1 F, dd, J = 163.3, 13.5 Hz). MS (EI) m/z; 310, 267, 195, 115, 91. Anal. Calcd for $C_{19}H_{29}F_2N_3O_2Si$: C, 57.41; H, 7.35; N, 10.57. Found: C, 57.30; H, 7.43; N, 10.44.

(2*R*,1'*S*,2'*S*)-2-Acetylamino-2-(2'-acetoxymethyl-3',3'-difluoro)cyclopropylethyl acetate (12-Major). Colorless prisms. mp 99.2-100.5 °C. $[\alpha]_D^{25.6}$ +12.1 (*c* 0.86, $CHCl_3$). IR ($CHCl_3$) ν, cm^{-1}; 3313, 1738, 1655, 1540. ^{1}H-NMR (400 MHz, $CDCl_3$) δ; 1.71 (1 H, m), 1.81 (1 H, ddd, J = 19.9, 7.4, 7.2 Hz), 1.97 (3 H, s), 2.03 (3 H, s), 2.07 (3 H, s), 4.06-4.20 (5 H, m), 6.13 (1 H, br). ^{13}C-NMR (100.6 MHz, $CDCl_3$) δ; 20.6, 23.1, 25.6 (dd, J = 10.8, 10.7 Hz), 28.0 (dd, J = 10.4, 10.2 Hz), 46.3,

60.06, 60.1, 64.8, 113.2 (dd, J = 287.1, 287.1 Hz), 169.5, 170.67, 170.7. ^{19}F-NMR (376.5 MHz, $CDCl_3$) δ; -75.3 (1 F, dd, J = 165.1, 12.9 Hz), -74.5 (1 F, dd, J = 165.2, 12.9 Hz). MS (EI) m/z; 294 (M^+), 252, 234. Anal. Calcd for $C_{12}H_{17}F_2NO_5$: C, 49.15; H, 5.84; N, 4.78. Found: C, 49.69; H, 5.95; N, 4.67.

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13. It was reported that conjugate addition of allylsilane with 4-substituted *N*-crotonoyloxazolidinone catalyzed by TiCl4 proceeds in highly diastereoselective manner through the bidentatedly co-ordinated transition state. It should be noted that the sense of asymmetric induction in the reaction of **5a** with **6** described here, was different from that of allylsilane reaction. see: Wu, M.-J.; Wu, C.-C.; Lee, P.-C. *Tetrahedron Lett.* **1992**, *33*, 2547-2548.

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Synthesis of (2*R*, 3*S*)- or (2*S*, 3*R*)-2-Amino-3-trifluoromethyl-3-hydroxy-alkanoic Acid Derivatives (Threonine and *allo*-Threonine Analogs) from Enantiopure 4,4,4-Trifluoro-3-hydroxybutanoic Acid

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Laboratorium für Organische Chemie der Eidgenössischen Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland.

Abstract: The title compounds are prepared from the readily available enantiopure 6-alkyl- or 6-aryl-2-*tert*-butyl-6-trifluoromethyl-1,3-dioxan-4-ones with *cis* disposition of the *tert*-butyl and trifluoromethyl groups. Lithium enolates of these dioxanones are added to di-*tert*-butyl-azo-dicarboxylate to give exclusively the hydrazino derivatives formed by electrophilic attack from the face opposite to the *tert*-butyl and trifluoromethyl groups. Methanolysis of the dioxanone ring, removal of the N-Boc groups, and hydrogenolysis of the hydrazine N, N bond give methyl esters of (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxybutanoic, (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxy-3-methyl-butanoic, (2*R*, 3*S*)-2-amino-3-trifluoromethyl-3-hydroxyheptanoic, and (2*R*, 3*S*)-2-amino-4,4,4-trifluoro-3-hydroxy-3-phenyl-butanoic acids in overall yields ranging from 10 to 50 %.

INTRODUCTION

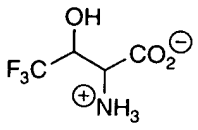
Fluorine containing analogs and derivatives of naturally occurring amino acids have proved to be of fundamental interest because of their intriguing chemical and biological properties[2]. A large number of fluoro amino acids have been synthesized, some of them exhibit high biological activities and are used as chemotherapeutic agents or in studies of the biosynthetic pathways of their corresponding proteinogenic counterparts[3]. Finally, they can be used as conformational modifiers in physiologically active proteins and enzymes[4].

In this context, the synthesis of trifluoromethyl substituted α-amino-β-hydroxy acids has attracted our attention not only because of their potential use in pharmaceuticals but also because of the challenge associated with their preparation in a stereoselective manner[5].

The first synthesis of racemic *threo* (*syn*) and *allo* (*anti*) 2-amino-4,4,4-trifluoro-3-hydroxybutanoic acids (**1**) was published in 1957 by *Walborsky* and *Baum*[6]. Their synthesis started from the readily available ethyl trifluoroacetoacetate which was diazotized with benzene diazonium chloride to give phenylhydrazone **2**. Reduction with $NaBH_4$, followed by saponification and catalytic hydrogenation gave the amino acids **1**.

A similar approach was chosen by *Scolastico* and his co-workers[7]. They nitrosated ethyl trifluoroacetoacetate with $NaNO_2$/AcOH to give the oxime which was O-methylated and reduced with $NaBH_4$ to give compound **3**. Reduction with zinc powder in formic acid produced a 1.5 : 1 mixture of *syn* and *anti* α-amino-β-hydroxy esters which could be separated by chromatography. Saponification of these esters led to the diastereoisomerically pure *syn*- and *anti*- amino acids **1**. In the same paper, the diastereoselective synthesis of *syn* 2-amino-4,4,4-trifluoro-3-hydroxybutanoic acid **1** is described, starting from dibenzylaminoacetate and ethyl trifluoroacetate to give the unstable β-ketoester by *Claisen* condensation followed by *in situ* reduction to the *syn* aminoester derivative **4**, which could readily be debenzylated with H_2/Pd(C).

Chart 1. Different intermediates from the synthesis of fluorine containing α-amino-β-hydroxybutanoic acids



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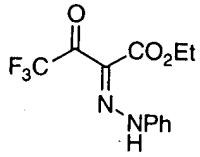

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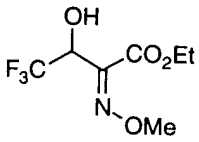

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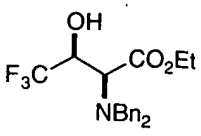

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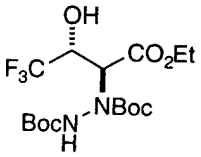

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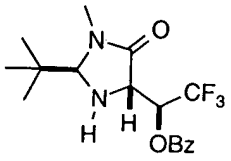
Guanti [8]



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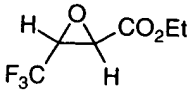
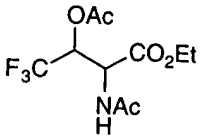
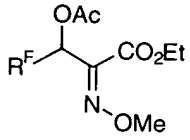
Seebach [9]



7
v.d.Bussche, Seebach [10]



8
Kitazume [11]



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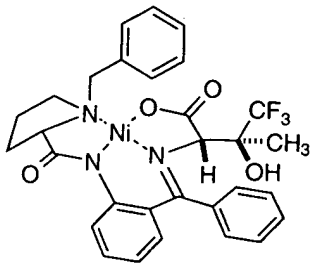

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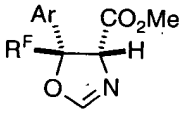
Belokon, Soloshonok [13]

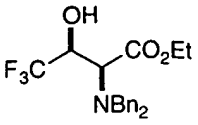


11
Hayashi [14]

In another diastereoselective synthesis furnishing *anti* -**1**, the electrophilic amination of β-hydroxy acids *via* the dianion with DBAD (di-*tert*-butyl-azodicarboxylate) was used by *Guanti* and coworkers[8]. The α-(*N*,*N*'-bis(*tert*-butoxycarbonyl)-hydrazino ester **5** was obtained in a 87 : 13 ratio of *anti* and *syn* product. Deblocking with TFA, saponification and hydrogenolysis of the hydrochloride gave the diastereoisomerically pure *anti*-**1**. In our group, an enantioselective synthesis of (2*S*, 3*S*)-trifluorothreonine was achieved using (*S*)-1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one[9]. The Li enolate of this heterocycle reacts diastereoselectively with aldehydes to form aldol adducts. The benzoate **6** thus obtained with trifluoroacetaldehyde was hydrolysed with 6N HCl at 100 °C in 24 h to give the enantiopure derivative (2*S*, 3*S*)-**1**. Enantiomerically pure *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate was also prepared in our group[10] starting from the glycidic ester **7**. The epoxide was treated with trimethylsilyl azide and the aminoester was obtained after hydrogenation with H_2 / Pd-C.

Another approach towards enantiomerically pure threonines **1** is the resolution of racemates *via* enzymatic transformations. *Kitazume* and coworkers[11] obtained a 1 : 1 mixture of *syn* and *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate by aldol addition of the *Schiff* base from glycin and benzaldehyde to trifluoroacetaldehyde. Acylation with acetylchloride gave an easily separable mixture of *syn* and *anti*-**8**. These racemates could be resolved by enantioselective hydrolysis of the acetate groups with lipase MY (*Candida Cylindracea*). A slightly different method was used by *Fujisawa* and his coworkers[12]. They prepared their

'droxybutanoic acids



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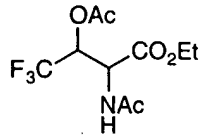
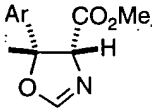
Scolastico[7]



8
Kitazume[11]



11
Hayashi[14]

mination of β-hydroxy
nd coworkers[8]. The α-
anti and *syn* product.
e diastereoisomerically
as achieved using (*S*)-
is heterocycle reacts
thus obtained with
ure derivative (2*S*, 3*S*)-
s also prepared in our
zide and the aminoester

lution of racemates *via*
nd *anti* ethyl 2-amino-
1 and benzaldehyde to
f *syn* and *anti*-**8**. These
h lipase MY (*Candida*
2. They prepared their

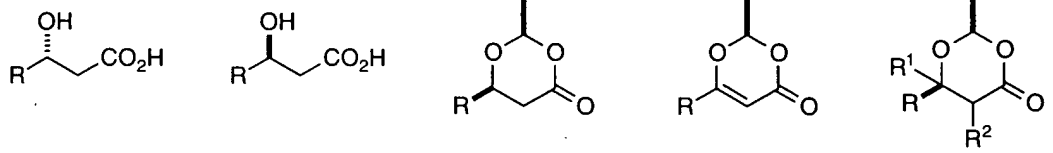
starting material **3** according to the method of *Scolastico*[7]. O-Acetylation led to the substrate **9** ($R^F = CF_3$) for enzymatic kinetic resolution by lipase-mediated hydrolysis (with *Amano* PS lipase). The resolved alcohols and acetates were readily transformed into the corresponding enantiopure threonines **1** using known procedures. Not only the derivatives **9** ($R^F = CF_3$) but also the ones having $R^F = CHF_2$, CH_2F and $CHCl_2$ could be resolved using this methodology.

The chiral Ni^{II} complex of a *Schiff* base derived from (*S*)-ortho-[*N*-(*N*-benzylprolyl)amino]-benzophenone (BPB) was used for enantioselective synthesis of several fluorinated α-amino-β-hydroxy acids by the groups of *Belokon* and *Soloshonok* [13]. Aldol addition of this complex to several F-containing aldehydes led to either *syn* or *anti* products, depending on the exact reaction conditions and on the base used. Addition of 1,1,1-trifluoroacetone produced adduct **10** which could be readily cleaved to give (2*S*, 3*S*)-3-(trifluoromethyl)-threonine in good yield. Enantiopure (2*S*, 3*S*)-4,4,4-trifluorothreonine **1** was obtained from trifluoroacetaldehyde and the chiral Ni complex by the same method.

Finally, eight different oxazolines **11** derived from the aldol reaction between fluoro substituted aryl ketones and isocyanoacetic acid catalyzed by transition metals have been published recently by *Hayashi* and coworkers[14]. The *cis* products depicted in formula **11** are formed predominantly. These oxazolines can be cleaved with conc. HCl / MeOH to the corresponding *syn* threonine esters (see Chart 1).

In the course of our work on β-hydroxy acids **12**, we have shown that (*R*)-3-hydroxybutanoic acid (**12**, R = CH_3, from polyhydroxy butanoate[15]) and (*S*)-3-hydroxybutyric acid (*ent*-**12**, R = CH_3, from ethyl acetoacetate by yeast reduction[16] or BINAP-Ru hydrogenation[17]) and other analogs can be transformed to *cis*-dioxanones of type **13** (R = CH_3[18], C_2H_5[18,19], CCl_3[20], CF_3[21]). Bromination with NBS, followed by hydrogenolysis gives enantiopure dioxinones **14**. However, the trifluoro derivative **14** (R = CF_3) cannot be prepared in this way because of the lack of reactivity of **13** (R = CF_3) with NBS (see below).

Chart 2. 3-Hydroxycarboxylic acids and the derived dioxanones and dioxinones

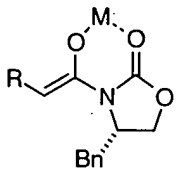


12 *ent* - **12** **13** **14** **15**

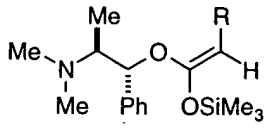
Several dioxanones of type **15** have been prepared from either compound **13** (leading to 2,5,6 trisubstituted dioxanones **15** having R^1 = H) or **14** (leading to 2,5,6,6 tetrasubstituted dioxanones **15**)[22], see Chart 2. The reaction sequence beginning with a chiral β-hydroxy acid **12** or ent-**12**, building up a second stereocenter diastereoselectively to give compounds of type **13**, followed by elimination of the original stereocenter with formation of **14** and then addition of a new substituent to this center in such a way, that the original orientation is regenerated as in dioxanones **15** (R^2 = H), is an application of the principle of "self-regeneration of stereogenic centers"[23]. The corresponding α- and/or β-branched β-hydroxy acids or esters can be obtained from these dioxanones by hydrolysis or alcoholysis under acidic conditions.

Inspired by the fact that chiral enolates (for some examples see Chart 3) can be converted stereoselectively to α-hydrazino derivatives with electrophilic aminating reagents such as DBAD[8, 24-29], we envisaged the synthesis of some 3-subtituted *allo*-threonines bearing a trifluoromethyl group by this method.

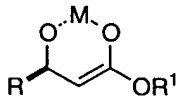
Chart 3. Some chiral enolates that have been diastereoselectively aminated with the azo-dicarboxylate DBAD



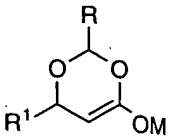
Evans[24]



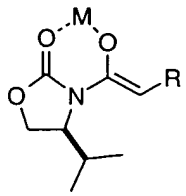
Gennari[25]



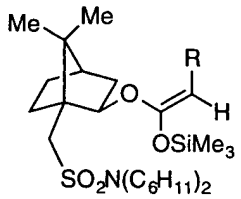
Guanti[8]



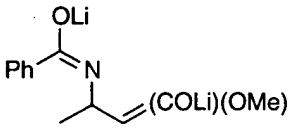
Genet[26]



Vederas[27]



Oppolzer[28]



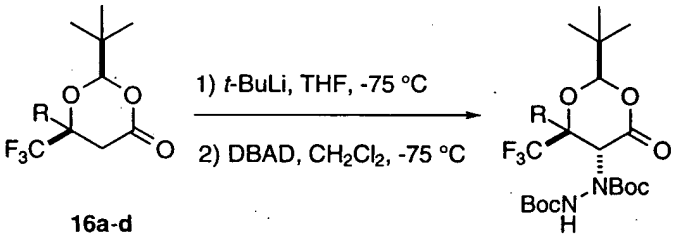
Seebach[29]

RESULTS

In this work, we chose the three trifluoro substituted dioxanones **16** (R = Me, Bu, Ph), which were prepared according to known procedures[30] by cuprate addition to the dioxinone **14** (R = CF_3). However, about a dozen of these compounds **16** are known, having R = CD_3, C_2H_5, C_3H_7, $CH(CH_3)_2$, $C(CH_3)_3$, CH_2-$CH{=}CH_2$, $CH_2C_6H_5$ and we believe that these could have been used analogously. Compound **14** (R = CF_3) can be prepared starting from the corresponding (*S*)-4,4,4-trifluoro-3-hydroxybutanoic acid (ent-**12**, R = CF_3) by acid catalyzed acetalization to the dioxanone **13** (R = CF_3)[21], which in turn is brominated in the 5-position, followed by dehydrohalogenation with DBU. Enantiopure acids **12** (R = CF_3) and ent-**12** (R = CF_3) are available on a 500 g scale from resolution of enantiomers by crystallization of the diastereoisomeric salts with (*R*)- and (*S*)-1-phenylethylamine[31].

Dioxanones **16a-d** were treated with *tert*-BuLi (other bases like LDA or LHMDS gave poorer results) at -75 °C, and then a cold (-75 °C) solution of DBAD in CH_2Cl_2 was added slowly to the enolate solution. Usually the reactions were complete after a few minutes and the hydrazino dioxanones **17a-d** were isolated in good yields and excellent diastereoselectivities (dr > 98 : 2), as outlined in Scheme 1.

Scheme 1.



Entry	Starting Material	R	Yield %
1	**16a**	H	97
2	**16b**	Me	86
3	**16c**	Bu	80
4	**16d**	Ph	71

The ^1H NMR spectra of compounds **17** obtained at room temperature in $CDCl_3$ were largely uninterpretable due to hindered rotation about the Boc groups. However, the corresponding spectra of **17a** and

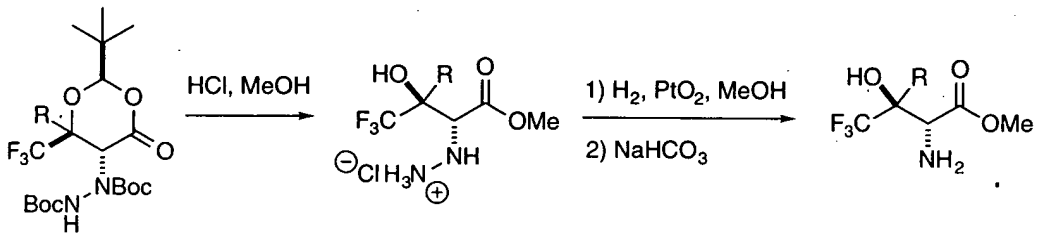
17b obtained in d_6-DMSO at 80 °C were dramatically simplified and could be readily analyzed. None of the other diastereoisomer could be detected either with ^1H- or ^{19}F-NMR spectroscopy. The relative configuration of the amination products could not be established at this stage. Compounds **17c** and **17d** were not isolated in analytically pure form, after flash chromatography (FC) there was still an impurity (a rotamer ?) present which could not be removed. Therefore, these two compounds were employed in the next step without further purification (see Experimental Part).

Treatment of **17a-d** with a saturated solution of HCl in methanol produced the α-hydrazino-β-hydroxy esters **18a-d** as the hydrochlorides. Depending upon the substituent R, this methanolysis had to be performed at elevated temperatures and with longer reaction times to achieve complete conversion. This led to the formation of significant amounts of by-products and lowered the yields of this step. The resulting hydrochlorides were directly hydrogenated with H_2/PtO_2 in methanol, without purification. Only small portions of these hydrochlorides were treated with saturated Na_2CO_3 solution and then purified by recrystallization, FC or sublimation to give the analytically pure α-hydrazino-β-hydroxy esters **18b-d** for full characterization.

It is noteworthy that **18a** could not be obtained by this procedure: As soon as the hydrochloride was treated with Na_2CO_3, an inseparable mixture of products was formed. Therefore, this compound was recrystallized in the form of the hydrochloride **18a**·HCl for analytical purposes. Aminoesters **19a-d** were isolated with the yields indicated in Scheme 2, by treating the crude products with saturated $NaHCO_3$ solution.

The enantiomer of **19a**, (2*S*, 3*R*)-methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (ent-**19a**) was also synthesized starting with ent-**16a**.

Scheme 2.



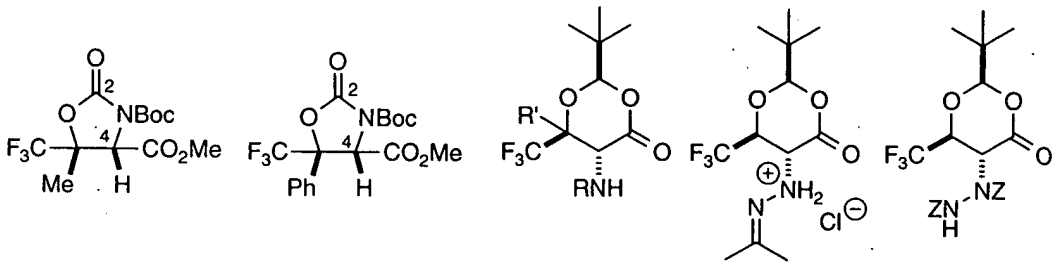
17a-d **18a-d · HCl** **19a-d**

Entry	Starting Material	R	Aminoester	Yield %	$[\alpha]_D^{RT}$ (EtOH)
1	**17a**	H	**19a**	37	- 25.0 (c: 1.15)
2	**17b**	Me	**19b**	47	- 25.5 (c: 1.46)
3	**17c**	Bu	**19c**	12	- 32.8 (c: 1.50)
4	**17d**	Ph	**19d**	11	- 28.5 (c: 0.94)

The relative configuration of aminoester **19a** was assigned by comparison of the coupling constant (J = 5.9 Hz) between H-C(2) and H-C(3) with that of the corresponding *anti* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (J = 5.7 Hz)[10]. The coupling constant of *syn* ethyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate is smaller (J = 3.1 Hz). This difference of coupling constants is qualitatively analogous to the situation in trifluoro-*allo*-threonine (J = 5.7 Hz) and trifluorothreonine (J = 1.8 Hz)[7, 9]. For the β-branched derivatives **19**, another configurational assignement had to be found. Serendipity came to our rescue: attempted protection of the NH_2 groups in **19b** and **19d** with excess di-*tert*-butyl-dicarbonate produced the N-Boc-oxazolidin-2-ones **20** and **21** in excellent yields (a manifestation of the Thorpe - Ingold[32] or "reactive-rotamer"

effect[33] !?). In these heterocycles **20** and **21** (Chart 4), there is a clear-cut positive nuclear-*Overhauser* effect (NOE) indicating *cis* position of Me / H and Ph / H. Irradiation with the resonance frequency of the CH_3-C(5) protons in **20** led to a positive NOE-effect on H-C(4) and irradiation with the resonance frequency of H-C(4) in **21** caused a positive NOE-effect on the ortho protons of the phenyl ring.

Chart 4. N-Boc-oxazolidin-2-ones from **19b** and **19d** and some dioxanones with N-subtituents in the 5-position.



20 **21** **22** **23** **24**

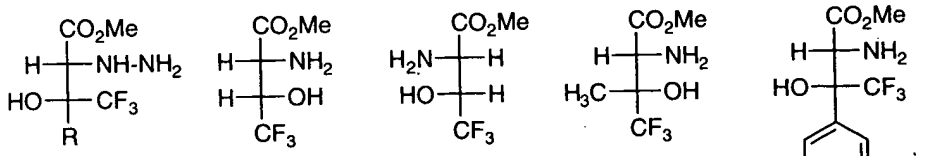
All attempts to prepare the 5-hydrazino- or 5-amino-substituted dioxanones **22** from the *N,N'*-di-Boc substituted hydrazino dioxanones **17** failed. Inseparable mixtures resulted from applications of the usual Boc deprotection procedure with compounds **17**. Experiments carried out to isolate the initially formed hydrazine **22** (R = NH_2, R' = H) and purify it by crystallization from acetone led to the hydrazone hydrochloride **23**, hydrogenation (H_2 / PtO_2) of which generated a product mixture from which no amino-dioxanone **22** (R, R' = H) could be isolated. In order to avoid acidic conditions, we also prepared the di-carbobenzyloxy-derivative **24** by *Michael* addition of the dioxanone **16a** to dibenzyl azodicarboxylate (61 % yield). However, hydrogenolytic deprotection (H_2 / Pd-C in EtOAc) again led to a terrible mixture of products. The recommended cleavage of hydrazine N, N bonds with SmI_2[34] also failed to afford the desired amino-dioxanone **22** (R = H) from **17a** or from **24**.

DISCUSSION

The reaction of the dioxanone enolates to give products **17** from attack of the azodicarboxylate trans to the CF_3 group exclusively is surprizing for two reasons. First of all, other 6,6-di-substituted dioxanone enolates of this type generally combine with electrophiles with poor diastereoselectivity[35,36]. Secondly, when going from R = H to R = CH_3 to R = Ph in **16**, there should be a decrease in selectivity with increasing *van der Waals* radius of these groups (1.2, 2.0 and *ca.* 5.3 Å) relative to CF_3 (2.7 Å)[37]. Since the conformation of the dioxanone enolate ring is presently unknown[35], it is difficult to interpret the effect observed.

From a synthetic point of view, we have described here simple methods for the preparation of new types of enantiopure amino- and hydrazino-hydroxy acid derivatives, see the *Fischer* projections in Chart 5. Both classes of derivatives should be interestingly incorporated into peptides to study their effects on the secondary structure and on physiological properties. So called aza-peptides containing a hydrazine unit in the backbone have been shown to be promising peptide analogs[38]. Also, the effect of the CF_3 group in the novel amino acids bearing a branched substituent, an OH and a CF_3 group in the 3-position will be important in peptides containing these residues: the OH group, embedded in a hydrophobic environment is a much stronger H-bond donor than in the non-fluorinated analogs (the pK_a values of CH_3CH_2OH and CF_3CH_2OH are 16[39] and 13[40], respectively).

Chart 5. *Fischer* projections of some of the prepared α-hydrazino- and α-amino-β-hydroxycarboxylic acid derivatives containing CF_3 groups.



18 **19a** ***ent*-19a** **19b** **19d**

Acknowledgements: We thank Dr. M. Gautschi for supervising some of the experiments described here. Generous supply of ethyl trifluoroacetoacetate from the *LONZA AG* (CH-Visp) and of pivalaldehyde from *BASF AG* (D-Ludwigshafen) as well as financial support from *SANDOZ PHARMA AG* (CH-Basel) are gratefully acknowledged. We thank J. Matthews and A. K. Beck for their help in preparing this manuscript.

EXPERIMENTAL

General. Abbreviations: THF (tetrahydrofuran), *t*-BuLi (*tert*-butyllithium), DBAD (di-*tert*-butyl-azodicarboxylate), DMAP (dimethylaminopyridine), rt (room temperature, *ca.* 22 °C), FC (flash chromatography). Solvents and reagents: ether was distilled over Na wire, THF was distilled over K under Ar, CH_2Cl_2 was dried over molecular sieves 4Å. The solution of *t*-BuLi (*ca.* 1.55M in pentane) was used as purchased and its content was titrated with *sec*-BuOH[41]. The solvents used for work-up and purification were distilled at normal pressure. Dioxanones **16** were prepared according to published procedures[30]. FC[42]: performed on silica gel (230 - 400 mesh, *Merck*). M.p.: *Büchi* 510, uncorrected. Optical rotations $[\alpha]_D^{RT}$: *Perkin-Elmer* 241 polarimeter, in 10 cm cells. ^{1}H NMR spectra: *Bruker WM* 300 (300 MHz) or *Varian XL* 300 (300 MHz), δ in ppm relative to TMS, *J* in Hz. ^{13}C NMR: *Bruker WM* 300 (75 MHz) or *Varian XL* 300 (75 MHz), δ in ppm relative to TMS, *J* in Hz.^{19}F NMR: *Varian XL* 300 (282.2 MHz) or *Varian Gemini* 300 (282.2 MHz), δ in ppm relative to $CFCl_3$, *J* in Hz. If not otherwise marked, the spectra were recorded at rt in $CDCl_3$. Mass spectra: *Hitachi-Elmer RMU-6M* or *VG Tribrid*, peak intensities are given as percentage of the base peak in parantheses. IR: *Perkin-Elmer 983* and *Perkin-Elmer 1600 FTIR*, absorptions are reported in cm^{-1}. Elemental analyses were performed by the Microanalytical Service Laboratory of ETH-Zürich.

General Procedure for the reaction of dioxanones 16[30] with DBAD: GP I. A solution of 20 mmol of the appropriate dioxanone in 50 ml THF was cooled to -75 °C under Ar. *t*-BuLi (14.2 ml, 22 mmol) was added slowly by syringe while keeping the temperature below -70 °C. The solution became yellow upon addition of the final drops. After stirring for 20 min at -75 °C, a cold (-75 °C) solution of DBAD (4.6 g, 20 mmol) in 125 ml CH_2Cl_2 was added *via* teflon cannula. The resulting solution was kept at -75 °C for a further 40 min and then quenched by the addition of 75 ml of saturated NH_4Cl solution. This mixture was allowed to warm to 0 °C, approximately 15 ml of water were added to dissolve the precipitated NH_4Cl and the aqueous layer was extracted twice with portions of 100 ml CH_2Cl_2, the combined organic extracts were dried over $MgSO_4$ and the solvent was removed under reduced pressure.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (17a). Following **GP I**, dioxanone **16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and DBAD (4.6 g, 20 mmol). After work-up, the yellow oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (8.84 g, 97 %) was isolated, which, according to ^{1}H NMR, was essentially pure. Recrystallization (from pentane) of a small sample yielded the analytically pure compound. M.p.: 115.0-116.5 °C; $[\alpha]_D^{RT}$ = +19.3 (c = 0.90, EtOH); IR (KBr): 3380*w*, 3330*m*, 2980*m*, 2940*w*, 1740*s*, 1695*s*, 1480*m*, 1410*m*, 1395*m*, 1370*s*, 1355*m*, 1340*m*, 1305*m*, 1290*s*, 1275*s*, 1265*s*, 1245*s*, 1200*s*, 1155*s*, 1135*s*, 1095*m*, 990*s*; ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 0.95 (*s*, 9H, *t*-Bu), 1.42 (*s*, 18H, *t*-Bu), 4.74-4.81 (*m*, H-C(6)), 4.87 (*d*, *J* = 9.1, H-C(5)), 5.30 (*s*, H-C(2)), 8.70 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 23.34 (CH_3), 27.71 (CH_3), 27.95 (CH_3), 34.70 (C), 56.16 (CH), 73.40 (*q*, *J* (C,F) = 31.5), 80.41 (C), 82.28 (C), 105.96 (CH), 122.86 (*q*, *J* (C,F) = 281.0), 153.65 (C), 155.19 (C), 163.02 (C); MS: 457 (1, $[M+1]^+$), 345 (7), 300 (20), 243 (48), 199 (56), 87 (25), 71 (19), 69 (34), 59 (31), 58 (42), 57 (100), 56 (36), 55 (21), 43 (45), 41 (65), 39 (35), 29 (55), 28 (50). Anal. Calcd. for $C_{19}H_{31}F_3N_2O_7$ (456.45): C, 50.00; H, 6.85; N, 6.14; F, 12.49; Found: C, 50.12; H, 7.08; N, 6.13; F, 12.31.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-methyl-6-trifluoromethyl-1,3-dioxan-4-one (17b). Following **GP I**, dioxanone **16b** (1.60 g, 6.7 mmol) was treated with *t*-BuLi (4.9 ml, 7.4 mmol) and DBAD (1.53 g, 6.7 mmol) in 40 ml of CH_2Cl_2. After usual work-up, the resulting colorless oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (3.31 g, 99 %) was isolated, which, according to ^1H NMR, was essentialy pure. FC (ether/pentane 1:3) yielded the analytically pure compound (2.71 g, 86 %). M.p.: 68.0-70.0 °C; $[\alpha]_D^{RT}$ = +18.8 (c = 1.04, EtOH); IR (KBr): 3380*w*, 3310*w*, 2980*m*, 2940*w*, 2880*w*, 1750*s*, 1730*s*, 1485*m*, 1460*m*, 1405*m*, 1395*m*, 1370*s*, 1350*m*, 1310*s*, 1280*s*, 1245*s*, 1170*s*, 1105*s*, 1035*m*, 1005*m*; ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 0.93 (*s*, *t*-Bu), 1.41 (*s*, *t*-Bu), 1.43 (*s*, *t*-Bu), 1.63 (*s*, CH_3), 4.88 (*s*, H-C(5)), 5.28 (*s*, H-C(2)), 8.60-9.15 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 13.19 (CH_3), 22.81 (CH_3), 27.16 (CH_3), 27.40 (CH_3), 33.75 (C), 58.35 (CH), 79.00 (*q*, *J* (C,F) = 30.0), 80.02 (C), 82.08 (C), 100.91 (CH), 123.98 (*q*, *J* (C,F) = 284.5), 154.45 (C), 161.77 (C); MS: 471 (2, $[M+1]^+$), 314 (42), 301 (30), 257 (95), 213 (90), 184 (22), 139 (33), 87 (31), 71 (18), 69 (23), 57 (100), 43 (18), 41 (60), 39 (15), 29 (14), 28 (21). Anal. Calcd. for $C_{20}H_{33}F_3N_2O_7$ (470.48): C, 51.06; H, 7.07; N 5.95; Found: C, 51.32; H, 7.26; N, 5.86.

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-6-butyl-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (17c). Following **GP I**, dioxanone **16c** (3.05 g, 10.8 mmol) was treated with *t*-BuLi (7.7 ml, 11.9 mmol) and DBAD (2.56 g, 10.8 mmol) in 75 ml of CH_2Cl_2. After usual work-up, the resulting yellow solid was carefully dried *in vacuo* (a sticky foam!) whereby 6.0 g of a yellowish, glassy product was obtained, which was purified by FC (ether/pentane 1:9) to give a colorless, amorphous solid (4.45 g, 80.4 %). This material was used in the next step without further purification. ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 0.83-0.93 (*m*, 3H), 0.97 (*s*, 9H), 1.22-1.55 (*m*, 6H), 1.43 (*s*, 9H), 1.45 (*s*, 9H), 5.02, 5.26, 5.57, 5.71, 5.80 (5*s*, 3H).

(2*R*,5*R*,6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(*tert*-butyloxycarbonyl)-hydrazino)-6-trifluoromethyl-6-phenyl-1,3-dioxan-4-one (17d). Following **GP I**, dioxanone **16d** (2.57 g, 8.5 mmol) was treated with *t*-BuLi (6.9 ml, 9.4 mmol) and DBAD (1.96 g, 8.5 mmol) in 60 ml of CH_2Cl_2. After usual work-up, the resulting yellow oil was carefully dried *in vacuo* (a sticky foam!). This mixture was purified by FC (ether/pentane 1:3) to give of a colorless foam (3.20 g, 70.7 %). This material was used in the next step without further purification. ^1H NMR (300 MHz, d_6-DMSO, 80 °C): 1.06, 1.09 (2*s*, 9H), 1.36, 1.39. 1.47 (3*s*, 18H), 3.49, 3.58, 3.61, 3.70 (4*s*, 1H), 5.26, 5.68, 5.75, 5.80, 5.86 (5*s*, 2H), 7.40-7.62 (*m*, 5H).

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxybutanoate hydrochloride (18a·HCl). Dioxanone **17a** (6.85 g, 15 mmol) was placed in a 250 ml flask and treated with 150 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at 0 °C for 3 h (monitored by TLC) and after this time, a clear solution was obtained. After removing the solvent under reduced pressure **18a**·HCl (3.54 g, 98 %) was obtained as a yellow powder. A small portion was recrystallized from ethyl acetate/methanol (95:5) to give a colorless powder. M.p.: 161.0 °C (decomp.); $[\alpha]_D^{RT}$ = +13.3 (c = 1.09, EtOH); IR (KBr): 3230*br.*, 3120*br.*, 2960*m*, 2940*m*, 1730*s*, 1585*m*, 1510*m*, 1440*m*, 1375*m*, 1350*m*, 1325*m*, 1290*s*, 1260*m*, 1240*s*, 1210*m*, 1170*s*, 1130*s*, 1115*s*, 1080*m*, 950*m*; ^1H NMR (300 MHz, CD_3OD): 3.83 (*s*, CH_3), 4.05 (*d*, *J* = 4.9, H-C(2)), 4.42 (*qd*, *J* = 7.0, 4.9, H-C(3)), 4.88 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 53.41 (CH_3), 62.61 (CH), 71.00 (*q*, *J* (C,F) = 31.5), 125.60 (*q*, *J* (C,F) = 283.5), 170.23 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -76.36 (*d*, *J* = 7.0); MS: 202 (14), 143 (68), 125 (78), 105 (55), 103 (100), 78 (34), 71 (94), 69 (24), 59 (20), 51 (32), 43 (71), 36 (66), 31 (59), 29 (27), 28 (99); Anal. Calcd. for $C_5H_{10}ClF_3N_2O_3$ (238.59): C, 25.17; H, 4.22; N, 11.74; Found: C, 25.28; H, 4.24; N, 11.70.

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxy-3-methylbutanoate (18b). Dioxanone **17b** (7.70 g, 16.4 mmol) was placed in a 250 ml flask and treated with 160 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at rt for 8 h (monitored by TLC) and after this time, a clear solution was obtained. After removing the solvent under reduced pressure, the hydrochloride **18b**·HCl (5.50 g) was obtained as a yellow powder. This product was used in the hydrogenation step without further purification. A small amount (200 mg) was dissolved in 15 ml of saturated Na_2CO_3 solution and 15 ml ether and the aqueous layer was extracted twice with 30 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. Recrystallization from ethyl acetate/ether (95:5) yielded a colorless solid **18b**. M.p.: 121.0-122.0 °C (decomp.); $[\alpha]_D^{RT}$ = -20.5 (c = 1.15, EtOH); IR (KBr): 3330*s*, 3290*m*, 2960*m*, 1730*s*, 1610*w*, 1440*m*, 1385*w*, 1350*m*, 1325*m*, 1275*s*, 1220*s*, 1200*s*, 1190*s*, 1155*s*, 1115*s*, 1080*s*, 960*m*; ^1H NMR (300 MHz, CD_3OD): 1.46 (*d*, *J* = 1.0, CH_3), 3.64 (*s*, H-C(2)), 3.77 (*s*, OCH_3), 4.85 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 19.28 (CH_3), 52.65 (CH), 70.60 (CH_3), 74.76 (*q*, *J* (C,F) = 29.5), 127.14 (*q*, *J* (C,F) = 285.5), 173.02 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -80.47 (*s*); MS: 217 (5, $[M+1]^+$), 157 (12), 139 (24), 119 (17), 103 (94), 71 (100), 69 (12), 59 (11), 43 (95), 42 (12), 31 (19), 29 (12); Anal. Calcd. for $C_6H_{11}F_3N_2O_3$ (216.15): C, 33.34; H, 5.13; N, 12.96; Found: C, 33.31; H, 5.24; N, 13.00.

(2*R*, 3*S*)-Methyl 2-hydrazino-3-hydroxy-3-trifluoromethylheptanoate (18c). Dioxanone **17c** (4.25 g, 8.3 mmol) was placed in a 250 ml flask and treated with 100 ml of a cold saturated solution of HCl in methanol. The suspension was heated to reflux, whereby a clear solution was formed, and heating was

continued for 12 h (monitored by TLC). After this time a yellow supension was obtained. Filtration trough celite, followed by removal of the solvent under reduced pressure furnished the hydrochloride **18c**·HCl (1.96 g) as a yellow powder. This product was used in the hydrogenation step without further purification. A small portion (230 mg) was dissolved in 10 ml of saturated Na_2CO_3 solution and 20 ml ether, the aqueous layer was extracted three times with 20 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent was evaporated. FC (pentane/ether 1:3) and subsequent sublimation (0.02 Torr/50 °C) gave the colorless solid **18c**. M.p.: 71.5-72.5 °C; $[\alpha]_D^{RT}$ = -6.8 (c = 1.00, EtOH); IR (KBr): 3430*br.*, 3335*s*, 3295*m*, 2960*m*, 2880*m*, 1725*s*, 1615*w*, 1465*m*, 1435*m*, 1345*m*, 1320*m*, 1305*m*, 1260*m*, 1220*s*, 1210*s*, 1185*s*, 1145*s*, 1110*m*, 990*m*, 970*m*; ^{1}H NMR (300 MHz): 0.95 (*t*, *J* = 7.2, CH_3), 1.24-1.70 (*m*, 4H), 1.78-1.98 (*m*, 2H), 2.80-4.94 (*br.*, 4H, OH, NH), 3.71 (*s*, H-C(2)), 3.81 (*s*, OCH_3); ^{13}C NMR (75 MHz): 13.92 (CH_3), 22.89 (CH_2), 24.41 (CH_2), 31.02 (CH_2), 52.64 (CH_3), 68.23 (CH), 74.92 (*q*, *J* (C,F) = 27.0), 125.79 (*q*, *J* (C,F) = 288.0), 170.79 (C); ^{19}F NMR (282.2 MHz): -78.16 (*s*); MS: 259 (0.4, $[M+1]^+$), 199 (3), 181 (4), 171 (2), 159 (2), 139 (1), 126 (1), 103 (100), 88 (4), 71 (64), 69 (3), 43 (13), 28 (16); Anal. Calcd. for $C_9H_{17}F_3N_2O_3$ (258.23): C, 41.86; H, 6.64; N, 10.85; Found: C, 42.17; H, 6.85; N, 10.43.

(2*R*, 3*S*)-Methyl 4,4,4-trifluoro-2-hydrazino-3-hydroxy-3-phenylbutanoate (18d). Dioxanone **17d** (3.20 g, 6 mmol) was placed in a 250 ml flask and treated with 100 ml of a cold saturated solution of HCl in methanol. The suspension was stirred at rt for 24 h (monitored by TLC) and the solvent was removed under reduced pressure to give the hydrochloride **18d**·HCl (1.80 g) as a yellow powder. This product was used in the hydrogenation step without further purification. A small portion (180 mg) was dissolved in 10 ml of saturated Na_2CO_3 solution and 20 ml ether, the aqueous layer extracted three times with 20 ml portions of ether. The combined organic layers were dried over $MgSO_4$ and the solvent evaporated. FC (pentane/ether 1:2) and subsequent sublimation (0.03 Torr/90 °C) gave the hydrazinoester **18d** as colorless needles. M.p.: 100.0-101.2 °C; $[\alpha]_D^{RT}$ = -13.9 (c = 1.44, EtOH); IR (KBr): 3430*br.*, 3350*m*, 3320*m*, 2955*w*, 1745*s*, 1735*s*, 1615*w*, 1495*w*, 1450*m*, 1435*m*, 1360*m*, 1310*m*, 1265*s*, 1220*s*, 1175*s*, 1075*m*, 1045*m*, 965*m*, 950*w*; ^{1}H NMR (300 MHz): 2.70-5.10 (*br.*, 4H, OH, NH), 3.84 (*s*, OCH_3), 4.14 (*s*, H-C(2)), 7.36-7.46 (*m*, 3 *arom.* H), 7.59-7.72 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 52.73 (CH_3), 66.87 (CH), 77.94 (*q*, *J* (C,F) = 28.0), 122.52 (C), 126.27 (CH), 128.00 (*q*, *J* (C,F) = 281.0), 128.46 (CH), 128.97 (CH), 135.25 (C), 172.95 (C); ^{19}F NMR (282.2 MHz): -76.84 (*s*); MS: 279 (0.5, $[M+1]^+$), 219 (3), 201 (4), 184 (3), 174 (2), 132 (2), 127 (2), 105 (28), 103 (100), 88 (3), 77 (26), 71 (72), 69 (5), 43 (15), 28 (23); Anal. Calcd. for $C_{11}H_{13}F_3N_2O_3$ (278.23): C, 47.49; H, 4.71; N, 10.07; Found: C, 47.45; H, 4.71; N, 9.85.

General Procedure for the hydrogenation of the hydrazinoesters GP II. A mixture of 5 mmol of the appropriate hydrazinoester hydrochloride and a catalytic amount (1 mmol) of $PtO_2 \cdot H_2O$ in 15 ml of methanol was placed in a 50 ml flask, equipped with a magnetic stirrer and a balloon filled with H_2. The reaction was usually complete after 2-5 d (TLC). After filtration (celite), the solvent was removed under reduced pressure to give the crude aminoester hydrochlorides as brownish powders.

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (19a). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18a**·HCl (1.19 g, 5 mmol) was hydrogenated with 100 mg of $PtO_2 \cdot H_2O$ over 5 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted twice with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. FC (ethyl acetate/ether 1:1) of the colorless, amorphous product gave the aminoester **19a** (578 mg, 62 %) as fine needles. M.p.: 116.0-117.0 °C; $[\alpha]_D^{RT}$ = -25.0 (c = 1.15, EtOH); IR (KBr): 3390*m*, 3320*w*, 3080*br.*, 2960*w*, 2930*w*, 2820*br.*, 2720*br.*, 1730*s*, 1725*s*, 1585*m*, 1440*m*, 1390*w*, 1375*m*, 1340*m*, 1290*s*, 1265*m*, 1235*s*, 1200*s*, 1180*s*, 1165*s*, 1155*s*, 1125*s*, 1090*s*, 1025*s*; ^{1}H NMR (300 MHz, CD_3OD): 3.72 (*d*, *J* = 5.9, H-C(2)), 3.74 (*s*, CH_3), 4.19 (*qd*, *J* = 7.2, 5.9, H-C(3)), 4.86 (*br.*, OH, NH); ^{13}C NMR (75 MHz, CD_3OD): 52.70 (CH_3), 56.54 (CH), 72.52 (*q*, *J* (C,F) = 30.0), 126.24 (*q*, *J* (C,F) = 283.0), 173.51 (C); ^{19}F NMR (282.2 MHz, CD_3OD): -76.24 (*d*, *J* = 7.2); MS: 188 (35, $[M+1]^+$), 128 (100), 118 (11), 88 (93), 80 (56), 69 (9), 60 (21), 59 (65), 58 (17), 48 (14), 42 (12), 33 (61), 30 (35), 29 (34), 28 (67); Anal. Calcd. for $C_5H_8F_3NO_3$ (187.11): C, 32.10; H, 4.31; N, 7.49; F, 30.46; Found: C, 32.11; H, 4.40; N, 7.56; F, 30.42.

(2*S*, 3*R*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxybutanoate (ent-19a). Following **GP I**, dioxanone *ent*-**16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and DBAD (4.6 g, 20 mmol). After work-up the yellow oil was carefully dried *in vacuo* (a sticky foam!) whereby a yellowish, glassy product (9.25 g, 97%) was isolated which, according to ^{1}H NMR, was essentialy pure. This product was treated with 100 ml of a cold saturated solution of HCl in methanol. The solution was held at 0 °C for 5 h (monitored by TLC), the solvent was removed under reduced pressure and the hydrochloride (5.52 g) was obtained as a yellow powder. Using **GP II**, this material was hydrogenated in 60 ml of methanol with 1.2 g of $PtO_2 \cdot H_2O$ over 24 h. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted three times with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent removed under reduced pressure. FC (ether) of the yellow oil afforded the aminoester *ent*-**19a** (1.39 g, 37 %) as a colorless solid. M.p.: 32.5-33.7 °C; $[\alpha]_D^{RT}$ = +25.5 (c = 1.02, EtOH).

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxy-3-methylbutanoate (19b). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18b**·HCl (5.6 g, ca. 16 mmol) was hydrogenated in 50 ml of methanol with 273 mg of $PtO_2 \cdot H_2O$ over 3 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted twice with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Bulb-to-bulb distillation (0.01 Torr/50 °C) of the yellow oil gave the aminoester **19b** (1.62 g, 50.3 %) as a colorless solid. M.p.: 32.0-33.2 °C; $[\alpha]_D^{RT}$ = -25.5 (c = 1.46, EtOH); IR ($CHCl_3$): 3420*m*, 3345*w*, 2955*m*, 1745*s*, 1605*w*, 1460*m*, 1450*m*, 1440*m*, 1405*m*, 1380*m*, 1345*m*, 1275*s*, 1180*s*, 1155*s*, 1090*s*, 1020*w*, 995*m*, 945*w*; ^{1}H NMR (300 MHz): 1.54 (*q*, *J* = 1.0, CH_3), 2.10-3.60 (*br.*, 3H, OH, NH_2), 3.45 (*d*, *J* = 1.0, H-C(2)), 3.79 (*s*, OCH_3); ^{13}C NMR (75 MHz): 19.91 (CH_3), 52.67 (CH_3), 59.21 (CH), 72.90 (*q*, *J* (C,F) = 27.5), 125.79 (*q*, *J* (C,F) = 288.0), 172.25 (C); ^{19}F NMR (282.2 MHz): -79.18 (*t*, *J* = 1.0); MS: 202 (2, $[M+1]^+$), 142 (45), 89 (10), 88 (100), 74 (11), 69 (4), 43 (19), 33 (25), 28 (28), 15 (8); Anal. Calcd. for $C_6H_{10}F_3NO_3$ (201.14): C, 35.83; H, 5.01; N, 6.96; Found: C, 35.54; H, 4.70; N, 6.50.

(2*R*, 3*S*)-Methyl 2-amino-3-trifluoromethyl-3-hydroxyheptanoate (19c). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18c**·HCl (1.73 g, ca. 5.8 mmol) was hydrogenated in 30 ml of methanol with 120 mg of $PtO_2 \cdot H_2O$ over 3 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 50 ml saturated $NaHCO_3$ solution /50 ml ether. The aqueous layer was extracted three times with 50 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. FC (ether/pentane 1:2) followed by bulb-to-bulb distillation (0.01 Torr/50 °C) of the oil gave the aminoester **19c** (160.7 mg, 11.4 %) as a colorless oil. $[\alpha]_D^{RT}$ = -32.8 (c = 1.50, EtOH); IR ($CHCl_3$): 3415*w*, 3345*br.*, 2960*m*, 2935*m*, 2875*w*, 1745*s*, 1615*w*, 1455*w*, 1435*m*, 1410*m*, 1320*m*, 1275*s*, 1260*s*, 1180*s*, 1150*s*, 1110*m*, 1095*m*, 1015*m*; ^{1}H NMR (300 MHz): 0.95 (*t*, *J* = 7.2, CH_3), 1.28-1.65 (*m*, 4H), 1.83-1.92 (*m*, 2H), 1.20-2.20 (*br.*, 2H, NH_2), 3.60 (*s*, H-C(2)), 3.78 (*s*, OCH_3), 5.01-5.62 (*br.*, 1H, OH); ^{13}C NMR (75 MHz): 13.95 (CH_3), 22.98 (CH_2), 24.47 (CH_2), 30.91 (CH_2), 52.63 (CH_3), 55.91 (CH), 74.69 (*q*, *J* (C,F) = 26.0), 126.09 (*q*, *J* (C,F) = 288.0), 172.08 (C); ^{19}F NMR (282.2 MHz): -78.07 (*s*); MS: 244 (4, $[M+1]^+$), 184 (15), 174 (4), 127 (4), 88 (100), 74 (14), 69 (3), 57 (16), 41 (12), 33 (19), 29 (19), 28 (25), 27 (10); Anal. Calcd. for $C_9H_{16}F_3NO_3$ (243.22): C, 44.44; H, 6.63; N, 5.76; Found: C, 44.55; H, 6.94; N, 5.69.

(2*R*, 3*S*)-Methyl 2-amino-4,4,4-trifluoro-3-hydroxy-3-phenylbutanoate (19d). Using the general procedure **GP II**, the hydrazinoester hydrochloride **18d**·HCl (347 mg, 1 mmol) was hydrogenated in 20 ml of methanol with 50 mg of $PtO_2 \cdot H_2O$ over 4 d. After evaporation of the solvent, the resulting powder was dissolved in a mixture of 20 ml saturated $NaHCO_3$ solution /20 ml ether. The aqueous layer was extracted three times with 30 ml portions of ether, the combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The resulting colorless oil (273 mg, according to ^{1}H NMR analysis a mixture of the desired aminoester **19d** and the corresponding cyclohexyl derivative) was purified by FC (ether/pentane 1:1) followed by bulb-to-bulb distillation (0.01 Torr/40 °C) to give the aminoester **19d** (112.0 mg, 38.8 %) as a colorless solid. M.p.: 83.5-84.5 °C; $[\alpha]_D^{RT}$ = -28.5 (c = 0.94, EtOH); IR (KBr): 3440*m*, 3395*m*, 3325*m*, 2950*w*, 1730*s*, 1715*s*, 1600*w*, 1455*m*, 1440*m*, 1335*m*, 1385*m*, 1270*m*, 1210*s*, 1180*s*, 1060*s*, 1075*m*, 970*m*; ^{1}H NMR (300 MHz): 1.05-1.80 (*br.*, 2H, NH_2), 3.83 (*s*, OCH_3), 4.06 (*s*, H-C(2)), 4.60-5.40 (*br.*, OH), 7.36-7.50 (*m*, 3 *arom.* H), 7.58-7.68 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 52.89 (CH_3), 56.61 (CH), 78.53 (*q*, *J* (C,F) = 28.5), 124.92 (*q*, *J* (C,F) = 288.0), 126.48 (CH), 128.64 (CH), 129.03 (CH), 134.76 (C), 173.64 (C); ^{19}F NMR (282.2 MHz): -76.41 (*s*); MS: 264 (0.4, $[M+1]^+$), 204 (8), 186 (4), 166 (3), 117 (5), 105 (18), 89 (48), 88 (100), 77 (15), 74 (14), 69 (3), 57 (11), 33 (16), 28 (21); Anal. Calcd. for $C_{11}H_{12}F_3NO_3$ (263.21): C, 50.20; H, 4.60; N, 5.32; Found: C, 50.26; H, 4.79; N, 5.15.

(4*R*, 5*S*)-3-(*tert*-Butyloxycarbonyl)-5-methyl-5-trifluoromethyl-4-(methoxycarbonyl)-oxazolidin-2-one (20). The aminoester **19b** (1.0 g, 5 mmol) was dissolved in 15 ml of CH_2Cl_2 and DMAP[43] (61 mg) and di-*tert*-butyldicarbonate (2.4 g, 11 mmol) were added. After 30 min at rt, the clear yellow solution was evaporated under reduced pressure. FC (ether/pentane 1:3) of the resulting yellow solid gave **20** (1.1 g, 73 %), wich was sublimed (0.01 Torr/80 °C) for analytical purposes. M.p.: 128.5-129.5 °C; $[\alpha]_D^{RT}$ = +29.0 (c = 0.99, EtOH); IR (KBr): 2980*w*, 1845*s*, 1820*s*, 1770*s*, 1735*m*, 1455*w*, 1430*m*, 1395*m*, 1370*s*, 1315*s*, 1260*s*, 1220*s*, 1210*s*, 1160*s*, 1110*s*, 1070*s*, 1020*m*, 975*m*, 960*m*; ^{1}H NMR (300 MHz): 1.52 (*s*, *t*-Bu), 1.79 (*d*, *J* = 1.0, CH_3), 3.83 (*s*, OCH_3), 4.61 (*s*, H-C(4)); ^{13}C NMR (75 MHz): 21.48 (CH_3), 27.81 (CH_3), 53.35 (CH_3), 63.42 (CH), 78.53 (*q*, *J* (C,F) = 32.5), 85.75 (C), 122.54 (*q*, *J* (C,F) = 284.0), 148.03 (C), 148.52 (C), 165.42 (C); ^{19}F NMR (282.2 MHz): -78.46 (*s*); MS: 312 (0.9), 268 (1), 254 (4), 228 (14), 168 (11), 104 (5), 86 (3), 69 (1), 59 (18), 57 (100), 43 (6), 41 (15), 28 (13); Anal. Calcd. for $C_{12}H_{16}F_3NO_6$ (327.26): C, 44.04; H, 4.93; N, 4.28; Found: C, 44.00; H, 4.85; N, 4.13.

(4*R*, 5*S*)-3-(*tert*-Butyloxycarbonyl)-5-trifluoromethyl-5-phenyl-4-(methoxycarbonyl)-oxazolidin-2-one (21). The aminoester **19d** (30 mg, 0.11 mmol) was dissolved in 1 ml of CH_2Cl_2 and DMAP[43] (2.5 mg) and di-*tert*-butyldicarbonate (52 mg, 0.24 mmol) were added. After 1 h at rt, the clear colorless solution was evaporated under reduced pressure. FC (ether/pentane 1:4) of the resulting oil gave **21**

(39.7 mg, 95 %) as a colorless liquid. ^{1}H NMR (300 MHz): 1.49 (*s*, *t*-Bu), 3.94 (*s*, OCH_3), 5.08 (*s*, H-C(4)), 7.49-7.52 (*m*, 3 *arom.* H), 7.69-7.72 (*m*, 2 *arom.* H); ^{13}C NMR (75 MHz): 27.76 (CH_3), 53.60 (CH_3), 64.71 (CH), 77.20 (*q*, *J* (C,F) = 32.0), 85.84 (C), 121.89 (*q*, *J* (C,F) = 284.5), 126.02 (CH), 129.11 (CH), 130.54 (CH), 133.50 (C), 147.80 (C), 148.17 (C), 165.72 (C); ^{19}F NMR (282.2 MHz): -75.78 (*s*).

(2*R*, 5*R*, 6*S*)-5-(Isopropylidene-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one hydrochloride (23). In a 50 ml, two necked flask, a solution of hydrazino dioxanone **17a** (2.28 g, 5 mmol) and *tert*-butanol (1.12 g) in 20 ml CH_2Cl_2 was cooled to 0 °C. HCl gas was bubbled into the solution for 1 h. The resulting yellow supension was evaporated and the residue (1.36 g) was dissolved in a small amount of ether. A white solid was precipitated by the addition of pentane. After filtration, the white residue (800 mg) was dissolved in 50 ml acetone, heated to reflux and then cooled in an ice bath. The white crystals were filtered and dried *in vacuo* to give **23** (450 mg, 27 %). M.p.: 165.0-167.0 °C (decomp.); $[\alpha]_D^{RT}$ = +24.5 (c = 0.96, EtOH); IR (KBr): 3420*br.*, 3140*m*, 2965*m*, 2620*br.*, 1755*s*, 1690*w*, 1485*m*, 1430*m*, 1400*m*, 1370*m*, 1360*m*, 1280*s*, 1240*s*, 1225*s*, 1200*s*, 1155*s*, 1085*s*, 1040*m*, 995*s*, 955*m*; ^{1}H NMR (300 MHz, d_6-DMSO): 0.95 (*s*, *t*-Bu), 2.02 (*s*, CH_3), 2.13 (*s*, CH_3), 4.43 (*d*, *J* = 9.9, H-C(5)), 5.04 (*dq*, *J* = 9.9, 6.0, H-C(6)), 5.48 (*s*, H-C(2)), 8.20-11.00 (*br.*, 1H, NH); ^{13}C NMR (75 MHz, d_6-DMSO): 17.64 (CH_3), 23.21 (CH_3), 23.32 (CH_3), 34.51 (C), 54.35 (CH), 73.29 (*q*, *J* (C,F) = 30.5), 105.89 (CH), 122.94 (*q*, *J* (C,F) = 281.0), 157.95 (C), 167.19 (C); ^{19}F NMR (282.2 MHz, d_6-DMSO): -74.93 (*d*, *J* = 6.0); MS: 298 (24), 297 (100), 239 (13), 211 (14), 166 (15), 165 (7), 154 (5), 123 (6), 71 (14), 69 (3), 57 (12), 56 (21); Anal. Calcd. for $C_{12}H_{20}ClF_3N_2O_3$ (332.74): C, 43.32; H, 6.06; N, 8.42; Found: C, 43.31; H, 5.92; N, 8.36.

(2*R*, 5*R*, 6*S*)-2-(*tert*-Butyl)-5-(*N*,*N*'-bis-(benzyloxycarbonyl)-hydrazino)-6-trifluoromethyl-1,3-dioxan-4-one (24). Following **GP I**, dioxanone **16a** (4.53 g, 20 mmol) was treated with *t*-BuLi (14.2 ml, 22 mmol) and dibenzyl azodicarboxylate (8.36 g, 28 mmol) in 100 ml of CH_2Cl_2. After work-up, the viscous oil was carefully dried for 12 h *in vacuo* whereby a yellowish oil (12.0 g) was isolated. FC (ether/pentane 1:3) gave 4.81 g (61% yield) of an amorphous compound. Recrystallization (from pentane/ether 1:1) of a small sample yielded the analytically pure compound **24** as colorless crystalls. M.p.: 123.5-124.0 °C; $[\alpha]_D^{RT}$ = +30.2 (c = 1.03, EtOH); IR (KBr): 3290*br.*, 2960*m*, 1755*s*, 1585*w*, 1495*m*, 1485*m*, 1455*m*, 1405*m*, 1370*m*, 1340*s*, 1275*s*, 1240*s*, 1220*s*, 1195*s*, 1145*s*, 995*s*, 695*s*; ^{1}H NMR (300 MHz, d_6-DMSO, 80 °C): 0.93 (*s*, *t*-Bu), 4.88 (*dq*, *J* = 9.4, 5.5, H-C(6)), 4.95-5.17 (*m*, 5H, -CH_2-Ph, H-C(5)), 5.31 (*s*, H-C(2)), 7.27-7.33 (*m*, 10 *arom.* H), 9.50-9.80 (*br.*, NH); ^{13}C NMR (75 MHz, d_6-DMSO, 80 °C): 23.28 (CH_3), 34.60 (C), 56.30 (CH), 66.68 (CH_2), 68.20 (CH_2), 72.86 (*q*, *J* (C,F) = 31.0), 106.12 (CH), 122.70 (*q*, *J* (C,F) = 281.0), 127.18-128.44 (*arom.* CH), 135.51 (C), 136.12 (C), 154.73 (C), 156.25 (C), 163.02 (C); MS: 525 (8, $[M+1]^+$), 424 (22), 423 (80), 271 (14), 215 (29), 182 (11), 181 (64), 107 (13), 92 (70), 91 (100), 77 (11), 69 (7), 65 (35), 57 (28), 41 (17), 39 (12); Anal. Calcd. for $C_{25}H_{27}F_3N_2O_7$ (524.49): C, 57.25; H, 5.19; N, 5.34; Found: C, 57.12; H, 5.27; N, 5.25.

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Fluoroolefin Containing Dipeptide Isosteres as Inhibitors of Dipeptidyl Peptidase IV(CD26)

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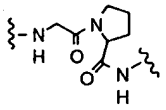
Abstract: (Z)-(*S*)Ala-Ψ[CF=C]-(*RS*)-Pro containing *N,O*-diacylhydroxamic acid type protease inhibitors have been prepared for the study of the influence of prolylamide bond geometry on the inhibition of dipeptidyl peptidase IV(CD26). The synthesis is based upon the use of *tert*-butyl α-fluoro-α-trimethylsilylacetate in a variation of the Peterson olefination procedure to construct the necessary functionalized fluoroolefin.

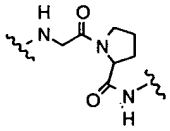
Prolyamides play a fundamental role in establishing the structure and function of peptides and proteins. The structural features unique to prolyamides are often critical to enzymatic recognition of proteins containing those residues.[1] In particular, the conformation around the P_1 and P_2-position[2] can be very important for the

$$H_3^+N-P_2\overset{\downarrow}{-}Pro-P_{1'}-P_{2'}-$$

catalytic activity of proline specific peptidases.[3] It has previously been postulated that proline specific endopeptidase (EC 3.4.21.26) and dipeptidyl peptidase IV (EC 3.4.14.5, DPP IV, CD26)[4] possess a high conformational specificity for a *trans* P_2-Pro bond.



trans



cis

DPP IV, discovered in 1966,[5] is a transmembrane serine peptidase found in a variety of human tissues and organs.[6] In particular DPP IV, when expressed on the surface of $CD4^+$ T-cells is identical with the CD26 antigen and is considered to be a lymphocyte activation marker.[7] Although the involvement of DPP IV in the immune response and regulation of lymphocyte activation has been implicated, the mechanism of the involvement is not clear. DPP IV has also been reported to be involved with the infection of T-cells with the human immunodeficiency virus[9] but this report has been questioned.[10]

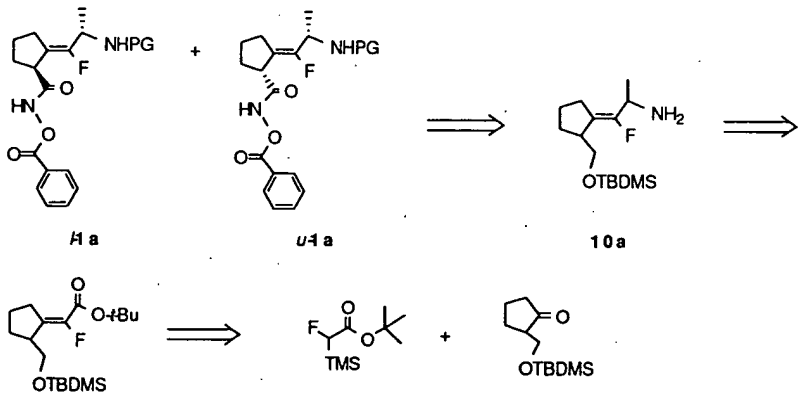
As a cell surface activation marker of lymphocytes,[11] failure to observe CD26 implies a reduced immune response.[12] The presence of DPP IV is associated with the capacity of cells to produce interleukin-2 (IL-2) and to proliferate strongly in response to mitogen stimulation.[13] Importantly binding of monoclonal antibodies to CD26 suppresses IL-2 production.[13b] CD26 modulation also can lead to enhanced cell proliferation proceeded by an increase in Ca^{2+} moblization.[14] CD26 is physically associated with CD45 (which

regulates T-cell activation pathways through protein tyrosine phosphatase action) apparently modulating the activity of CD45 by affecting the accessibility of critical substrates with the result that the CD2 / CD3 path amplifies the immune response.[15] Obviously inhibition of CD26 may critically effect T-cell activation and function and may potentially have therapeutic utility in the modulation of the rejection of transplanted tissue by the host organism.

Relatively few effective inhibitors of DPP IV have been reported.[16] Given the requirement for a DPP IV substrate to have a free *N*-terminal amino group, it is not surprising that the inhibitors which have been reported generally suffer from instability. The cyclization reaction of the free *N*-terminal amino group with the reactive site of the inhibitor does however require the molecule to assume the *cis* conformation, the conformation that was previously proposed to be unreactive with the DPP IV.[3] In order to obviate this mode of inactivation and to rigorously examine the *cis-trans* selectivity of DPP IV we prepared a series of conformationally constrained fluoroolefin dipeptide isosteres. The fluoroolefin dipeptide isostere was proposed as early as 1984[17] as a superior isoelectronic and isosteric replacement for the amide bond. Various synthetic approaches have been employed in the preparation of fluoroolefin containing dipeptide surrogates.[18] While theoretical studies have strongly supported the original hypothesis behind introduction of the fluoroolefin amide surrogate,[19] it was only recently that an experimental assessment of binding of these mimics was possible.[20]

RESULTS AND DISCUSSION

Synthetic Plan. We chose to prepare an acyl hydroxamic acid type inhibitor[21] to expedite our initial investigation of the importance of the P_2-Pro amide bond geometry. A brief retrosynthetic analysis for the target compound **1a** is outlined in Scheme 1. This strategy relies on the efficient construction of the fluoroolefin moiety by the Peterson olefination reaction followed by the further elaboration of the terminal functional groups to approach the target substances.

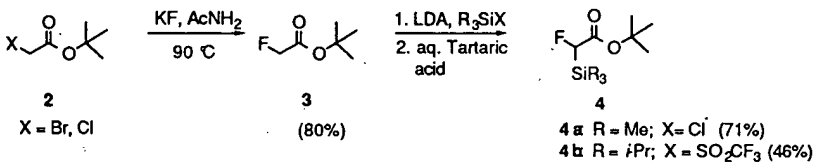


Scheme 1

Peterson Fluoroolefination Reaction. A key precursor for the entire synthetic sequence is a fluoroolefin such as **6a** bearing the appropriate latent functionalities . Although many methods have been used to construct fluoroolefins in the preparation of a variety of biologically active materials,[22] relatively few examples of these synthetic approaches have general applicability. The Peterson olefination reaction was first employed by our laboratory to prepare the fluoroolefin moieties of various fluorine-containing compounds.[23] Our previous

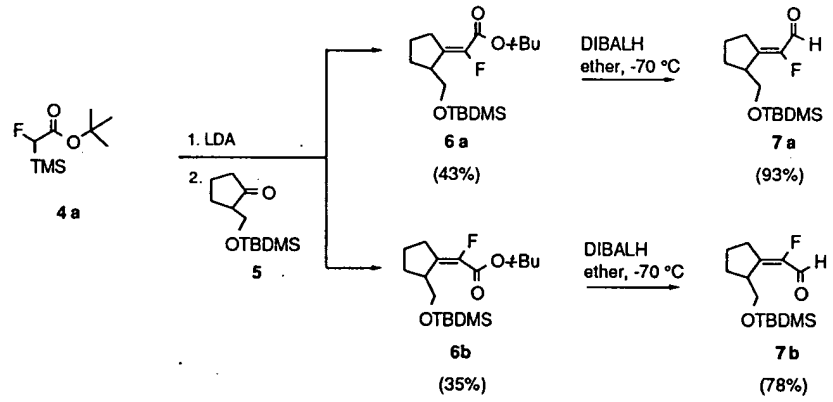
studies described the Peterson olefination of aryl aldehydes with 2,4,6-trimethylphenyl α-fluoro-α-trimethylsilylacetate led to the highly stereoselective formation of (*Z*)-fluoroalkenoates. In contrast, the reaction with aryl or alkyl ketones exhibited very low selectivity with (*E*)-fluoroalkenoates being formed in slight excess in most cases. The stereoselective potential of this reaction prompted us to extend the scope of this useful method for the preparation of fluoroolefins. Recently, an alternative route using a new α-fluoro-α-trialkylsilyl acetate, simple and convenient to prepare, was developed.[24] (Scheme 2)

As shown in Scheme 2 , treatment of commercially available *tert*-butyl α-chloroacetate or *tert*-butyl α-bromoacetate **2** with potassium fluoride easily yielded *tert*-butyl α-fluoroacetate **3** in 80% yield. The outcome of the direct *C*-silylation of **3** is highly depended on the molar ratio of the reagents employed, as well as the reaction temperature and time. It was found that *C,O*-bissilylation and Claisen condensation always accompanied the desired *C*-silylation reaction. After careful optimization, **4a** was formed in 71% yield by treatment of **3** with 4 equivalents of LDA and 6 equivalents of chlorotrimethylsilane at -78 °C. The purification of **4a** was achieved by fractional distillation where higher boiling point by-products were easily separated.



Scheme 2

Total Synthesis of Target Molecule **1a.** The choice of the amine protecting group for the target compound **1a** was a vexing problem. The desired protecting group had to be sufficiently labile so that it could be removed without affecting the hydroxamate functionality, also, ideally it should be compatible with standard *N*-terminal peptide synthesis protocols. Fortunately, Demuth[25] found that the *tert*-butoxycarbonyl (Boc) protecting group was removable by hydrochloric acid / acetic acid, conditions under which the hydroxamate functional group was uneffected.



Scheme 3

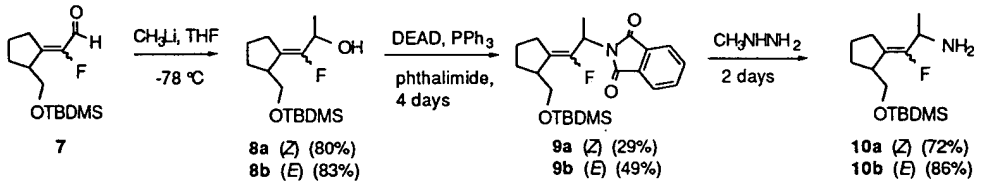
As shown in Scheme 3, the synthesis of the fluoroolefin began with Peterson olefination of the TBDMS-protected 2-(hydroxymethyl)cyclopentanone[26] **5** under our modified conditions employing *tert*-butyl α-fluoro-α-trimethylsilylacetate **4a**. The fluoroolefin product **6** was obtained as a 1.2 : 1 ratio of (*Z*): (*E*) isomers in 78% yield. The double bond isomers could be separated by column chromatography. Confirmation of the structural identity of the isomers was possible by comparison of the NMR spectra of the corresponding reduction product, aldehyde **7**, with the spectra reported in our earlier work.[23c] Earlier attempts to directly reduce the fluorinated α,β-unsaturated esters to the corresponding aldehydes with DIBALH in THF had been unsuccessful,[23c] the products being the corresponding primary alcohols. These results were consistent with an earlier report[27] on the reduction of nonfluorinated α,β-unsaturated esters. However, following the procedure of Wuts,[28] when **6a** or **6b** was treated with a slight excess of DIBALH (1.2 to 1.5 molar equivalents) in diethyl ether at -78 °C for 1 h, the corresponding aldehyde **7** was formed as nearly a single product in excellent yield. (Table 1)

Table 1. Reaction Conditions for Conversion of **6** to aldehyde **7**.

Esters	DIBALH Equivalents	Solvent	Ester **6** Reduction Products[a] Aldehyde **7** (%)	Alcohol (%)
6a	4.0	THF	10	87
6b	4.0	THF	9	84
6b	1.5	ether	78	12
6a	1.3	ether	89	4
6a	1.2	ether	93	0.2

a. Isolated yields after column chromatography.

Aldehyde **7** could then be converted to the desired α-amino-α-methyl moiety *via* several different synthetic approaches. Scheme 4 shows the practical synthetic route previously developed by our laboratory.[23c]

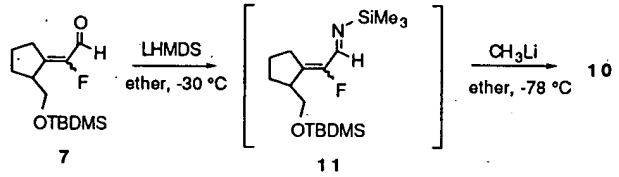


Scheme 4

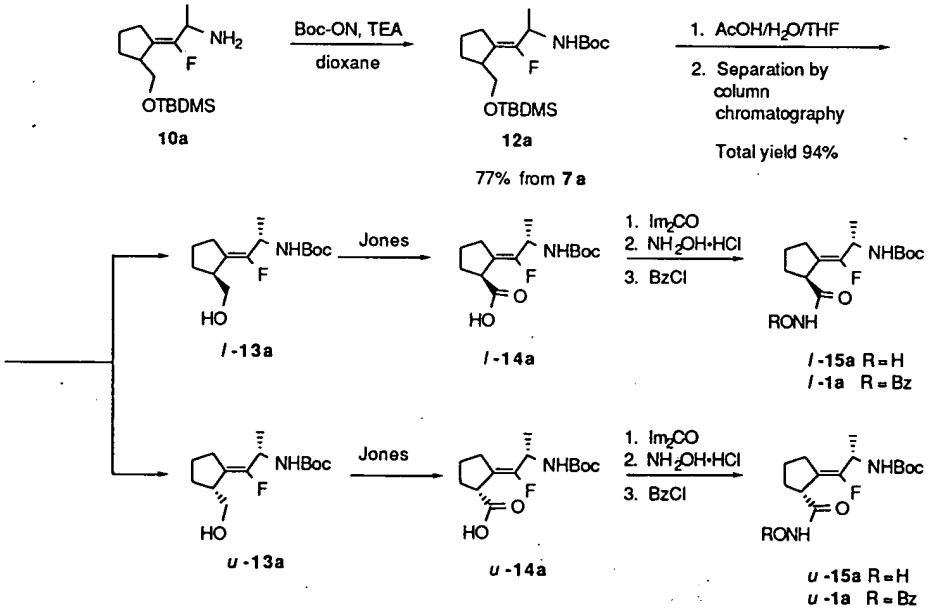
The selective 1,2-addition of methyllithium to aldehyde **7** was easily accomplished.[29] After purification by chromatography according to Still,[30] the combined yield of the separated diastereomers of the secondary alcohol **8** was 80%. Transformation of **8** to the protected amide **9** was carried out under standard Mitsunobu conditions over four days.[31] As could be anticipated, low yields resulted in both the (*E*) and (*Z*) cases (29% and 49%) probably as a result of the steric effect of secondary alcohol on the displacement reaction. Unfortunately, the phthalimide protecting group was not suitable in these cases because of the forcing conditions required for its removal; the phthalimide group could only be liberated by treatment of **9** with excess methylhydrazine at room

temperature for two days. The long reaction times and low yields of the Mitsunobu reaction when combined with the difficult deprotection resulted in depressingly low overall yields of amine **10**.

Literature precedent [32] for the direct alkylative amination of aldehydes encouraged us to develop a more efficient synthetic approach (Scheme 5). The sequential treatment of a nonenolizable aldehyde with lithium bis(trimethylsilyl)amide (LHMDS) followed by condensation with the desired organolithium or Grignard reagents in THF was reported to give the corresponding α-substituted alkyl amines,[32a] presumably *via* the intermediacy of a *N*-trimethylsilyl imine. The putative intermediate *N*-trimethylsilyl imines were not normally purified or characterized. Repeated attempts to form the desired amine **10** from aldehydes **7a** or **7b** under these conditions[19b,32] failed. Many unidentifiable products were generated as observed by ^{19}F NMR. After further investigation, it was found that the formation of the crucial intermediate **11** was highly dependent upon the reaction temperature employed and the choice of the solvent. Competitive vinylogous deprotonation of the imine by the organolithium or Grignard reagent to form the corresponding vinylogous azaenolate, appeared to be the major source of byproducts in this reaction.



Gratifyingly, the optimum conditions were found after extensive study. Treatment of aldehyde **7a** with LHMD (1.2 equiv.) in diethyl ether at -30 °C for 1 h, then subsequent addition of methyllithium (2.0 equiv.) in



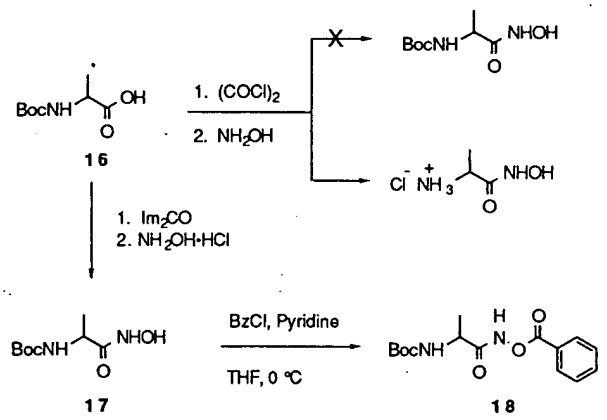
Scheme 5

ether at -78 °C followed by stirring for an additional hour afforded the desired amine **10a** in 93% yield as a 1.3:1 ratio of diastereomers. The observed ^{19}F resonances were consistent with those of amine products derived from the previously described synthetic route (Scheme 4). Interestingly, if the reaction was conducted under the same conditions in THF instead of diethyl ether, the desired product was formed in only very low yield.

Even though it was possible to separate the diastereomers of **10a** by chromatography, it was anticipated that it might be more convenient to delay the diastereomeric separation until preparation of the deprotected alcohol **13a**. Therefore, **10a**, as a mixture of diastereomers was protected using 2-(Boc-oxyimino)-2-phenylacetonitrile (Boc-ON) according to the standard procedure[33] in good yield (77%, overall from aldehyde **7a**).

Selective cleavage of the silyl ether **12a**, in the presence of the Boc-group, was accomplished by treatment with acetic acid-water-THF liberating the primary alcohol **13a** in 94% yield as a 1.2 : 1 ratio of diastereomers.[34] Following separation of the diastereomers by column chromatography, Jones oxidation of the alcohols *l*-**13a** and *u*-**13a**, respectively, yielded the corresponding crystalline carboxylic acids, *l*-**14a** and *u*-**14a**, without loss of the acid-sensitive Boc-group.

The final transformations necessary to form **1a** required the conversion of carboxylic acid **14a** to hydroxamic acid **15a**, and subsequent acylation of **15a** with benzoyl chloride. In a model study, we attempted to convert a model compound, *N*-Boc-alanine (**16**) to the acid chloride by using oxalyl chloride,[35] followed by hydroxylaminolysis of the crude acid chloride with hydroxylamine. The procedure failed when the hydrochloric acid generated during the reaction hydrolyzed the Boc-group (Scheme 6).



Scheme 6

However, hydroxamic acid **17** was readily formed in 78% yield from carboxylic acid **16** *via* addition of 1,1'-carbonyldiimidazole to form the reactive acylimidazole, which was subsequently condensed with hydroxylamine hydrochloride.[36] Boc-protected hydroxamic acid **17** was converted to the *N,O*-diacylhydroxylamine **18** in 94% yield by addition of equimolar amount of benzoyl chloride and pyridine.[35] One of the diastereomers **14a** was hydroxylaminated in the same manner to form the hydroxamic acid **15a** in 50% yield. Acylation of the **15a** with benzoyl chloride under the conditions described above formed the **1a** in 51% yield. We are currently optimizing the reaction conditions for each of these last two steps.

This synthesis can be easily adopted for the preparation of (*E*)-Ψ[CF=C] containing compounds as well. This flexible and efficient synthetic route can readily accommodate the introduction of other reactive functionality such as boronic acids common to effective serine protease inhibitors. Inhibition studies of these materials with DPP IV are in progress and will be reported elsewhere.

EXPERIMENTAL SECTION

General Methods. Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 Series FTIR spectrometer. All ^{1}H NMR spectra were recorded at 300 MHz on a Gemini-300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) or residual chloroform as the internal standard. All ^{13}C NMR spectra were recorded at 75.429 MHz on a Gemini XL-300 NMR spectrometer with $CDCl_3$ as solvent and tetramethylsilane (TMS) or residual chloroform as the internal standard. ^{19}F NMR spectra were recorded at 282.203 MHz on a Gemini XL-300 NMR spectrometer with $CDCl_3$ as solvent and chlorotrifluoromethane ($CFCl_3$) as the internal standard. Thin layer chromatography was performed with silica gel F_{254} (Merck) as the adsorbent on 0.2 mm thick, plastic-backed plates. The chromatograms were visualized under UV (254 nm), by staining with a 5% solution of phosphomolybdic acid in isopropanol followed by drying in an oven at 90 °C, or by spraying with a 95 : 5 mixture of 0.2% ninhydrin in *n*-butanol and 10% aqueous acetic acid followed by heating. Column chromatography was performed using silica gel 60 (70-230 mesh, Merck) and flash silica gel 60 (0.040-0.063 μm, 230-400 mesh, EM Science). Melting points were determined in open capillaries using a Büchi 510 melting point apparatus and are reported uncorrected. Boiling points are reported in degrees Centigrade at the indicated pressure in mm mercury (Hg) and are uncorrected.

***tert*-Butyl α-fluoroacetate (3).** To a mixture of acetamide (44.26 g, 750 mmol, recrystallized from MeOH/EtOH and dried) and potassium fluoride (43.58, 750 mmol, dried under vacuum using an Abderhalden apparatus at 110 °C for 24 h), was added *tert*-butyl α-chloroacetate **2** (46.58 g, 300 mmol). The mixture was heated to 90 °C and stirred well for at least 12 h to ensure complete conversion, which was then allowed to cool to room temperature. The reaction mixture was distilled under reduced pressure (71-72 °C / 145 mm Hg) to give pure **3** as colorless liquid (32.25 g, 80%). The further purification by the second distillation (131-133 °C / 760 mm Hg) might be needed to remove the trace amount of starting material **2**: Bp 131-133 °C (Lit.[37] 133-135 °C); IR (neat) 2982, 1762 (CO), 1444, 1396, 1370, 1314, 1162, 1082, 846 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -228.28 (t, J = 48.8 Hz); ^{1}H NMR ($CDCl_3$) δ 4.68 (d, J = 48.4 Hz, 2H), 1.48 (s, 9H).

***tert*-Butyl α-fluoro-α-trimethylsilylacetate (4a).** To a solution of diisopropylamine (33.4 mL, 240 mmol) in THF (120 mL), was added slowly *n*-butyllithium (95.4 mL, 240 mmol, 2.5 *M* solution in hexanes) at -30 °C. The solution was stirred for 15 min at -30 °C, then transferred via canula into the prepared solution of *tert*-butyl fluoroacetate **3** (8.00 g, 60 mmol) and chlorotrimethylsilane (45.7 mL, 360 mmol) in 320 mL of THF and 400 mL of pentane at -78 °C. The temperature was kept between -78 °C and -80 °C during the transfer, then warmed to 0 °C over a period of 3 hours. The mixture was immediately quenched with $NaHCO_3$ (120 mL) at 0 °C. The separated aqueous layer was extracted with ether (3 x 120 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated to a volume of 200 mL. Analysis of the ^{19}F NMR indicated a mixture of *C*- and *O*-bissilylated enol ether and monosilylated α-fluoro ester **4a**. Hydrolysis of this mixture with saturated tartaric acid aqueous solution (200 mL) at room temperature overnight yielded 7.33 g (71%) of *tert*-butyl α-fluoro-α-(trimethylsilyl)acetate **4a** after distillation: Bp 62-64 °C (30 mm Hg); IR (neat) 2956, 1749, 1253, 821 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -225.70 (d, J = 47.5Hz); ^{1}H NMR ($CDCl_3$) δ 4.53 (d, J = 47.9 Hz,

1H), 1.47 (s, 9H), 0.15 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 170.07 (d, J =19.2 Hz), 87.87 (d, J = 181.2 Hz), 81.74, 28.30, 2.92, 1.10, -3.71.

Peterson Olefination of 4a and TBDMS-protected 2-(hydroxymethyl)cyclopentanone (5). To a solution of diisopropylamine (2.4 mL, 17 mmol) in THF (105 mL), was added dropwise *n*-butyllithium (6.9 mL, 17 mmol, 2.5 *M* solution in hexane) at -25 °C. The solution was stirred for 15 min at -30 °C, then allowed to cool to -95 °C. *tert*-Butyl α-fluoro-α-trimethylsilyl acetate **4a** (3.10 g, 15.0 mmol) dissolved in THF (10 mL) was added to LDA solution and stirred for 40 min at -95 °C, followed by addition of 2-hydroxymethyl cyclopentanone derivative **5** (3.77 g, 16.5 mmol) in THF (10 mL). The reaction mixture was stirred for additional 10 min at -95 °C, and the cooling bath was removed. The reaction mixture was quenched with saturated NH_4Cl (25 mL) at 0 °C. The separated aqueous layer was extracted with hexanes (3 x 100 mL). The combined organic layers were dried with $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/CH_2Cl_2; 6 : 4) to give 2.18 g of the (*Z*)-fluoroolefin, **6a**, and 1.80 g of the (*E*)-fluoroolefin, **6b** (overall yield: 78%): TLC (50% CH_2Cl_2 in hexanes: R_f 0.46, **6a**; R_f 0.52, **6b**). (Z)-isomer, **6a**: IR (neat) 2950, 2863, 1718, 1679, 1477, 1368, 1342, 1256, 1098, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -125.43 (s); ^1H NMR ($CDCl_3$) δ 3.73 (dd, J = 9.6, 4.2 Hz, 1H), 3.46 (t, J = 8.7 Hz, 1H), 3.09 (m, 1H), 2.70-2.54 (m, 2H), 1.86-1.65 (m, 4H), 1.50 (s, 9H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 160.38 (d, J = 35.0 Hz), 142.87 (d, J = 246.3 Hz), 139.46 (d, J = 13.6 Hz), 81.91, 62.99 (d, J = 4.0 Hz), 45.93, 31.13, 28.55, 28.10, 25.83, 24.62, 18.22, –5.44, –5.54. (*E*)-isomer, **6b**: IR (neat) 2956, 2881, 1688, 1472, 1260, 1098, 1031, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$)δ -120.88 (s); ^1H NMR ($CDCl_3$) δ 3.62 (dd, J = 9.3, 3.9 Hz, 1H), 3.45 (t, J = 8.7 Hz, 1H), 3.35 (m, 1H), 2.51-2.42 (m, 2H), 1.74-1.64 (m, 4H), 1.52 (s, 9H), 0.87 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 159.88 (d, J = 35.6 Hz), 142.99 (d, J = 245.9 Hz), 139.99 (d, J = 14.8 Hz), 82.06, 64.03 (d, J = 4.5 Hz), 44.63, 30.16, 29.53, 28.08, 25.88, 22.65, 18.26, –5.40, –5.54. Anal. Calcd for $C_{18}H_{33}FO_3Si$: C, 62.75; H, 9.65. Found: C, 63.11; H, 9.94.

1-(1-Fluoro-2-oxoethylidene)-2-(*t*-butyldimethylsilyloxymethyl)cyclopentanes (7a and 7b). *tert*-Butyl ester **6a** (2.00 g, 5.80 mmol) was dissolved in dried diethyl ether (21 mL). The resulting solution was cooled to -78 °C, and diisobutylaluminum hydride (1.3 mL, 7.3 mmol) was added dropwise as 1 *M* solution in pentane (7.3 mL). The mixture was stirred at -78 °C for 1h and then quenched with H_2O (2 mL). The reaction mixture was allowed to warm to room temperature and stirred for an additional 1 h. The white solids were filtered and washed thoroughly with ether. The filtrate was dried over $MgSO_4$, concentrated *in vacuo*. The light yellow residue was submitted to a flash column chromatography using hexane/EtOAc (9 : 1) as eluent to provide the aldehyde **7a** (1.47 g, 93%): IR (neat) 2926, 2847, 2748, 1694, 1640, 1470, 1258, 1100, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -133.69 (d, J = 16.2 Hz); ^1H NMR ($CDCl_3$) δ 9.57 (d, J = 16.4 Hz, 1H), 3.74 (dd, J = 9.7, 4.0 Hz, 1H), 3.64 (dd, J = 9.7, 6.8 Hz, 1H), 3.20-3.10 (m, 1H), 2.84-2.60 (m, 2H), 2.30-1.65 (m, 4H), 0.84 (s, 9H), 0.01 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 182.26 (d, J = 29.1 Hz), 149.86 (d, J = 248.8 Hz), 147.58 (d, J = 11.2 Hz), 63.16 (d, J = 3.9 Hz), 45.82, 29.05, 28.29, 25.81, 25.16, 18.21, –5.49, –5.56. Anal. Calcd for $C_{14}H_{25}FO_2Si$: C, 61.72; H, 9.25. Found: C, 61.67; H, 9.15.

Except that using 1.5 equivalents of diisobutylaluminum hydride, the aldehyde **7b** was prepared in the same manner in 78% yield: IR (neat) 2954, 2856, 2740, 1742, 1688, 1640, 1472, 1258, 1098, 938 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -129.40 (d, J = 19.0 Hz); ^1H NMR ($CDCl_3$) δ 9.53 (d, J = 19.0 Hz, 1H), 3.59 (dd, J = 9.7, 6.0 Hz, 1H), 3.38 (t, J = 9.3 Hz, 1H), 3.28 (br q, J = 7.4 Hz, 1H), 2.64-2.58 (m, 2H), 1.90-1.60 (m, 4H),

0.83 (s, 9H), 0.02 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 182.76 (d, J = 24.7 Hz),151.21 (d, J = 250.2 Hz), 146.88 (d, J = 13.2 Hz), 64.80 (d, J = 3.5 Hz), 42.77 (d, J = 5.4 Hz), 29.54, 29.10, 25.78, 25.72, 18.23, –5.47, –5.56. Anal. Calcd for $C_{14}H_{25}FO_2Si$: C, 61.72; H, 9.25. Found: C, 61.64; H, 9.09.

1-[1-Fluoro-(2-hydroxy-2-methyl)ethylidene)-2-(*t*-butyldimethylsilyloxymethyl]cyclopentanes (8a and 8b). Methyllithium (3.1 mL, 4.6 mmol, 1.5 *M* solution in diethyl ether) was added dropwise to a solution of (*E*)-aldehyde, **7b** (0.70 g, 2.6 mmol) in THF (66 mL) at -78 °C under N_2. The reaction mixture was stirred at -78 °C for 90 min. After the cooling bath was removed, the mixture was stirred at room temperature for another hour, then recooled to 0 °C and quenched with 30 mL of H_2O. To this quenched mixture was added 150 mL of CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 (2 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. ^{19}F NMR analysis of the crude product show a 3.2 : 1 ratio of diastereomers which were separated by a column chromatography with hexane/EtOAc (9 : 1) to give 0.47 g of the major diastereomer, **8b'**, and 0.15 g of the minor isomer, **8b"** (total yield: 83%). **8b'**: IR (neat) 3416, 2956, 2858, 1712, 1472, 1388, 1362, 1256, 1172, 1094 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.40 (d, J = 24.4 Hz); ^{1}H NMR ($CDCl_3$) δ 4.44 (dq, J = 24.2 Hz, 1H), 3.51 (ddd, J = 10.0, 5.8, 1.8 Hz, 1H), 3.39 (t, J = 9.7 Hz, 1H), 2.83 (br q, J = 7.2 Hz, 1H), 2.47-2.27 (m, 2H), 1.81-1.45 (m, 4H), 1.31 (d, J = 6.0 Hz, 3H), 0.88 (s, 9H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.36 (d, J = 253.0 Hz), 121.18 (d, J = 17.0 Hz), 66.24 (d, J = 3.0 Hz), 64.62 (d, J = 30.4 Hz), 42.61 (d, J = 5.3 Hz), 29.83, 26.76 (d, J = 3.6 Hz), 26.08, 23.31, 18.68, 18.58 (d, J = 4.2 Hz), –5.53, –5.56. **8b"**: IR (neat) 3392, 2956, 2858, 1712, 1472, 1362, 1256, 1096, 1004, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -119.90 (d, J = 14.7 Hz); ^{1}H NMR ($CDCl_3$) δ 4.48 (br sext., J = 6.8 Hz, 1H), 3.71 (dd, J = 9.9, 5.4 Hz, 1H), 3.55 (t, J = 9.9 Hz, 1H), 3.11 (br q, J = 7.4 Hz, 1H), 2.82 (br s, 1H), 2.50-2.20 (m, 2H), 2.16-1.50 (m, 4H), 1.34 (d, J = 6.5 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.97 (d, J = 247.2 Hz), 119.41 (d, J = 16.8 Hz), 65.70 (d, J = 3.7 Hz), 65.45 (d, J = 35.0 Hz), 41.53 (d, J = 5.2 Hz), 29.61, 27.01 (d, J = 3.6 Hz), 25.93, 22.42, 20.70, 18.40, –5.51, –5.57. In the same method, **8a** was prepared in 80% yield as colorless oil. The major isomer, **8a'**: IR (neat) 3380, 2954, 2857, 1712, 1472, 1362, 1256, 1096, 836 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -132.05 (d, J = 25.8 Hz); ^{1}H NMR ($CDCl_3$) δ 4.47 (dq, J = 26.0, 6.6 Hz, 1H), 3.74 (dd, J = 9.8, 4.4 Hz, 1H), 3.37 (t, J = 9.6 Hz, 1H), 3.00-2.85 (m, 1H), 2.40-2.10 (m, 2H), 1.90-1.50 (m, 4H), 1.34 (d, J = 6.6 Hz, 3H), 0.87 (s, 9H), 0.03 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 153.30 (d, J = 249.2 Hz), 120.70 (d, J = 15.4 Hz), 65.33 (d, J = 29.5 Hz), 63.85 (d, J = 3.1 Hz), 43.50, 29.18, 28.20 (d, J = 4.9 Hz), 25.95, 24.55, 19.87 (d, J = 2.2 Hz), –5.45, –5.51.

***N*-Phthalimide-1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy)methyl] cyclopentanes (9a and 9b).** The major isomer, **8a'** (0.61 g, 2.1 mmol), triphenylphosphine (0.72 g, 2.7 mmol) and phthalimide (0.41 g, 2.7 mmol) in THF (20 mL) was treated dropwise with diethylazodicarboxylate (0.50 g, 2.73 mmol) as a 2 mL solution in THF at room temperature. After stirring at ambient temperature for 4 days, the solvent was evaporated *in vacuo*. The syrupy residue was dissolved in a minimum amount of CH_2Cl_2 and transferred to a column. Elution with hexane/EtOAc (9 : 1) yielded 0.427 g (49%) of **9b'** as yellow oil: IR (neat) 2954, 2856, 1778, 1716, 1470, 1380, 1254, 1094, 1004, 838 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -118.40 (d, J = 30.2 Hz); ^{1}H NMR ($CDCl_3$) δ 7.81 (dd, J = 5.4, 2.9 Hz, 2H), 7.68 (dd, J = 5.4, 3.1 Hz, 2H), 5.37 (dq, J = 29.9, 7.4 Hz, 1H), 3.49 (dd, J = 7.4, 2.4 Hz, 2H), 3.10-3.00 (m, 1H), 2.35-2.30 (m, 2H), 1.74 (d, J = 7.4 Hz, 3H), 1.70-1.52 (m, 4H), 0.91 (s, 9H), 0.091 (s, 3H), 0.089 (s, 3H). (*Z*)-isomer, **9a** was made in the

same manner in 29 %: ^{19}F NMR ($CDCl_3$) δ -119.14 (d, J = 24.4 Hz), -120.09 (d, J = 24.4 Hz); ^{1}H NMR ($CDCl_3$) δ 7.84-7.65 (m, 8H), 5.27-5.09 (m, 2H), 3.70 (dd, J = 9.9, 4.2 Hz, 1H), 3.66 (dd, J = 9.6, 3.9 Hz, 1H), 3.43 (t, J = 9.2 Hz, 1H), 3.34 (dd, J = 9.0 Hz, 1H), 3.00-2.85 (m, 2H), 2.38-2.27 (m, 4H), 1.67 (d, J = 6.3 Hz, 3H), 1.65 (d, J = 5.7 Hz, 3H), 1.79-1.53 (m, 8H), 0.86 (s, 9H), 0.76 (s, 9H), 0.015 (s, 6H).

1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy)methyl]cyclopentanes (10a and 10b). Method A (Scheme 4): Methylhydrazine (92 mg, 2.0 mmol) was added dropwise to a solution of **9b'** (84.0 mg, 0.20 mmol) in 4 mL of freshly distilled CH_2Cl_2. The reaction mixture was stirred at room temperature and monitored by TLC. After 48 hours, TLC analysis indicated that the reaction was complete. The solvent was evaporated and the residue was treated with 5 mL of EtOAc. The white solids were filtered and washed with EtOAc. Concentration of the filtrate gave a crude amine product, which was purified by a column chromatography (4% MeOH in CH_2Cl_2), affording free amine **10b'** (49 mg, 86%): IR (neat) 3376, 3303, 2956, 2858, 1710, 1637, 1472, 1256, 1099, 1006, 836, 786 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -129.09 (d, J = 24.4 Hz); ^{1}H NMR ($CDCl_3$) δ 3.39-3.28 (m, 3H), 2.77-2.69 (m, 1H), 2.36-2.23 (m, 2H), 1.82-1.58 (m, 6H), 1.28 (d, J = 6.5 Hz, 3H), 0.86 (s, 9H), 0.012 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 156.29 (d, J = 248.5 Hz), 118.81 (d, J = 14.7 Hz), 65.29 (d, J = 4.1 Hz), 46.07 (d, J = 25.8 Hz), 43.10 (d, J = 5.3 Hz), 29.41, 27.13, 27.08, 25.96, 23.28, 18.41, –5.32, –5.38. (*Z*)-isomer **10a** was prepared by following the same procedure in 72% yield.

Method B (Scheme 5): A hexane solution of *n*-butyllithium (1.5 mL, 3.8 mmol, 2.5 *M* solution in hexane) was slowly added to a solution of 1,1,1,3,3,3-hexamethyldisilazane (0.67 g, 4.2 mmol) in diethyl ether (32 mL) cooled in an ice-water bath. The cooling bath was removed and the solution was stirred at room temperature for 30 min. The mixture was cooled to -30 °C and to this lithium bis(trimethylsilyl)amide solution was added a solution of 0.87 g (3.2 mmol) of the aldehyde **7a** in 8 mL of ether. The mixture was stirred at -30 °C for 1 h, then cooled to -78 °C. The resulting solution containing *N*-trimethylsilyl imine was treated with methyllithium (4.3 mL, 6.40 mmol, 1.5 *M* solution in ether) at -78 °C. The mixture was stirred at -78 °C for 1 h and then at room temperature for an additional 2 h. The solution was cooled to 0 °C again, quenched with 32 mL of saturated aqueous NH_4Cl, and extracted with CH_2Cl_2 (4 x 50 mL). The combined extracts were dried ($MgSO_4$) and concentrated *in vacuo*. To remove some nonpolar impurities, the residue was subjected to a purification on a very short silica column using hexane/CH_2Cl_2 (1 : 1) as the eluent to give a 1.3 : 1 ratio of diastereomers, **10a** (0.86 g, 93%). The mixture of diastereomers was carried over to the next step without isolation: IR (neat) 3377, 3282, 2956, 2861, 1710, 1654, 1472, 1257, 1098, 838, 776 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -132.08 (d, J = 25.8 Hz), -132.08 (d, J = 27.1 Hz); ^{1}H NMR ($CDCl_3$) δ 3.73-3.56 (m, 2H), 3.37 and 3.33 (dt, J = 9.4, 9.6 Hz, 1H), 2.95-2.82 (m, 1H), 2.78-2.10 (m, 2H), 1.80-1.47 (m, 6H), 1.21 and 1.20 (d, J = 6.7, 6.7 Hz, 3H), 0.86 and 0.85 (s, 9H), 0.010 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 155.51 (d, J = 249.5 Hz), 155.33 (d, J = 248.7 Hz), 117.85 (d, J = 15.9 Hz), 117.74 (d, J = 15.9 Hz), 64.00 (d, J = 3.4 Hz), 63.96 (d, J = 3.4 Hz), 46 58 (d, J = 28.5 Hz), 46.47 (d, J = 28.5 Hz), 43.27, 29.27, 28.26 (dd, J = 5.5, 4.4 Hz), 28.19, 28.13, 25.90, 24.82, 24.58, 20.56, 20.12, 18.31, 18.28, –5.31, –5.36, –5.53.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene-2-(*t*-butyldimethylsilyloxy) methyl]cyclopentanes (12a). To a solution of amine **10a** (0.86 g, 3.0 mmol) in dioxane (60 mL) were added triethylamine (0.62 mL, 4.5 mmol) and 2-(*t*-butoxycarbonyloxyimino)-2-phenyl acetonitrile (Boc-ON) (0.88 g, 3.6 mmol). The mixture was stirred for 20 h at room temperature and the solvent was evaporated. Elution of

the crude by a slow column chromatography with hexane/EtOAc (20 : 1) yield 0.88 g of **12a** (77% from aldehyde **7a**): IR (neat) 3450, 3346, 2956, 2862, 1712, 1498, 1366, 1250, 1170, 1096, 1052, 838 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -130.09 (d, J = 24.4 Hz), -130.78 (d, J = 24.4 Hz); ^1H NMR ($CDCl_3$) δ 4.76 (br s, 1H), 4.47 (br d, J = 24.7 Hz, 1H), 3.68 and 3.63 (dd, J = 8.5, 4.5 Hz and 9.5, 4.5 Hz, 1H), 3.38 and 3.32 (t, J = 8.3, 9.6 Hz), 2.89 (m, 1H), 2.38 (m, 1H), 2.16 (m, 1H), 1.85-1.53 (m, 4H), 1.40 (s, 9H), 1.23 and 1.22 (d, J = 6.9, 6.9 Hz, 3H), 0.86 and 0.85 (s, 9H), 0.00 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 154.80, 154.77, 153.13 (d, J = 248.2 Hz), 119.68 (br s), 79.37, 63.90 (d, J = 3.6 Hz), 63.78 (d, J = 3.3 Hz), 43.39, 43.26, 29.31, 28.36, 25.91, 25.88, 24.79, 24.44, 18.75, 18.38, 18.29, 18.26, –5.37, –5.41, –5.45.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene)-2-(hydroxy)methyl] cyclopentanes (13a). A solution of **12a** (0.77 g, 2.0 mmol) in AcOH/H_2O/THF (100 mL, 13 : 7 : 3) was stirred for 16 h at room temperature. The solvent was then removed under vacuum. The yellow liquid residue was treated with solid $NaHCO_3$ until the mixture was slightly basic, and H_2O (8 mL) was added. The mixture was extracted with EtOAc (4 x 40 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by chromatography (hexane/EtOAc, 4 : 1) to provide 0.28 g of one diastereomer **13a'** (51%) and 0.23 g of the other isomer, **13a"** (43%). **13a'**: IR (neat) 3440, 3340 (br, s), 2976, 2872, 1692, 1518, 1453, 1366, 1248, 1168, 1054 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -130.50 (d, J = 28.5 Hz); ^1H NMR ($CDCl_3$) δ 4.74 (br s, 1H), 4.38 (br d, J = 28.5 Hz, 1H), 3.57 (d, J = 4.5 Hz, 2H), 2.97-2.88 (m, 1H), 2.49-2.35 (m, 1H), 2.28-2.13 (m, 1H), 1.92-1.51 (m, 5H), 1.40 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.97, 151.99 (d, J = 249.3 Hz), 119.17 (d, J = 14.7 Hz), 79.64, 64.13 (d, J = 3.8 Hz), 46.05 (d, J = 26.8 Hz), 43.45, 29.64, 28.41, 28.31, 24.85, 17.90. Data for **13a"**: ^{19}F NMR ($CDCl_3$) δ -129.28 (d, J = 29.8 Hz); ^1H NMR ($CDCl_3$) δ 4.80 (br s, 1H), 4.45 (br d, J = 27.0 Hz, 1H), 3.62 (dd, J = 10.5, 5.1 Hz, 1H), 3.44 (t, J = 9.2 Hz, 1H), 2.93 (m, 1H), 2.43 (m, 1H), 2.19 (m, 1H), 1.87 (m, 1H), 1.77-1.52 (m, 4H), 1.39 (s, 9H), 1.23 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 154.82, 152.67 (d, J = 248.1 Hz), 119.32 (d, J = 14.1 Hz), 79.50, 64.18 (d, J = 3.7 Hz), 46.62 (d, J = 29.5 Hz), 43.46, 29.39, 28.32, 28.13 (d, J = 5.3 Hz), 24.77, 18.63. Anal. Calcd for $C_{14}H_{24}FNO_3$: C, 61.52; H, 8.85. Found: C, 61.41; H, 8.99.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Carboxylic Acid (14a). Jones reagent (0.30 mL, 2.8 mmol) was dropwise added to a solution of alcohol **13a'** (0.15 g, 0.56 mmol) in dry acetone (9 mL) at 0 °C. The solution turned orange to greenish. The reaction mixture was stirred for 1 h at 0 °C, then quenched with H_2O (14 mL), extracted with EtOAc (3 x 30 mL). The extracts were dried over $MgSO_4$, filtered and concentrated *in vacuo*. Column chromatography (hexane/EtOAc, 3 : 2) yielded the carboxylic acid **14a'** (0.12 g, 73%) as a white solid: Mp 122-126 °C: IR (CH_2Cl_2) 3490-2567 (br, s), 3300, 3264, 2978, 2862, 1710, 1653, 1406, 1252, 1166, 1056, 910, 734 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.26 (d, J = 25.8 Hz); ^1H NMR ($CDCl_3$) δ 4.83 (br s, 1H), 4.47 (br d, J = 28.9 Hz, 1H), 3.48 (br s, 1H), 2.62-2.40 (m, 1H), 2.32-2.17 (m, 1H), 2.01-1.84 (m, 4H), 1.41 (s, 9H), 1.25 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 179.34, 154.99, 153.16 (d, J = 254.5 Hz), 117.79 (d, J = 13.9 Hz), 79.69, 45.59 (d, J = 30.0 Hz), 45.45, 31.65, 28.28, 28.09 (d, J = 3.8 Hz), 25.74, 18.00. The other diastereomer **14a"** was made in the same manner in 74% yield: Mp 98-103 °C; ^{19}F NMR ($CDCl_3$) δ -124.90 (d, J = 25.8 Hz); ^1H NMR ($CDCl_3$) δ 4.76 (br s, 1H), 4.49 (br d, J = 27.1 Hz, 1H), 3.52 (m, 1H), 2.60-2.47 (m, 1H), 2.41-2.26 (m, 1H), 2.08-1.81 (m, 4H), 1.41 (s, 9H), 1.27 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$) δ 179.68, 154.91, 153.20 (d, J = 251.4

Hz), 117.53 (d, J = 15.3 Hz), 79.64, 45.59 (d, J = 30.0 Hz), 45.22, 31.61, 28.35, 28.00 (d, J = 3.9 Hz), 25.76, 18.12. Anal. Calcd for $C_{14}H_{22}FNO_4$: C, 58.52; H, 7.72. Found: C, 58.19; H, 7.77.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Hydroxamic Acid (15a). Carboxylic acid **14a'** (80.0 mg, 0.28 mmol) was stirred with 1,1'-carbonyldiimidazole (49.7 mg, 0.31 mmol) in THF (3 mL) at room temperature for 18 hours in a flask fitted with a gas outlet. The reaction was monitored by TLC until no starting material **14a'** was detected. To the solution containing the active carbonyldiimide was then added NH_2OH•HCl (39.1 mg, 0.56 mmol). The resulting cloudy solution was stirred at room temperature for 9 h. The positive 5% $FeCl_3$ test indicated the formation of hydroxamic acid (deep purple color). The complete reaction mixture was diluted with 5 mL of H_2O, then extracted with diethyl ether (4 x 10 mL). The combined organic extracts were washed with 10 mL of H_2O, dried ($MgSO_4$) and concentrated. Purification by chromatography on silica gel (30 to 50% EtOAc in hexanes) gave 16.6 mg of hydroxamic acid **15a'** (20%) as off-white solid: IR (CCl_4) 3314, 3240, 2972, 2935, 1708, 1682, 1634, 1530, 1454, 1368, 1244, 1170, 1060 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -125.03 (d, J = 23.0 Hz); ^1H NMR ($CDCl_3$) δ 9.82 (br s, 1H), 4.71 (br s, 1H), 4.22 (dq, J = 25.9, 6.7 Hz, 1H), 3.58 (d, J = 2.4 Hz, 1H), 2.65-2.51 (m, 1H), 2.34-1.59 (m, 5H), 1.43 (s, 9H), 1.26 (d, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 169.11, 155.83, 152.65 (d, J = 254.5 Hz), 117.47 (d, J = 14.3 Hz), 80.67, 46.21 (d, J = 26.2 Hz), 44.93, 31.75, 28.27, 27.44 (d, J = 3.0 Hz), 24.48, 16.79. The other diastereomer **15a"** was prepared by the same procedure. Recrystallization from ethyl acetate gave pure **15a"** in 50% yield as white crystals: Mp 177-179 °C; ^{19}F NMR (CD_3OD) δ -122.74 (d, J = 25.8 Hz); ^1H NMR (CD_3OD) δ 4.86 (br s, 1H), 4.38 (dq, J = 27.1, 6.7 Hz, 1H), 3.60 (br s, 1H), 2.64-2.52 (m, 1H), 2.43-2.30 (m, 1H), 2.02-1.77 (m, 3H), 1.70-1.58 (m, 1H), 1.42 (s, 9H), 1.24 (d, J = 7.1 Hz, 3H); ^{13}C NMR (CD_3OD) δ 173.85, 157.36, 154.75 (d, J = 252.2 Hz), 119.31 (d, J = 15.3 Hz), 80.26, 46.92 (d, J = 25.2 Hz), 45.15, 32.84, 29.45 (d, J = 4.0 Hz), 28.76, 27.06, 17.71. Anal. Calcd for $C_{14}H_{23}FN_2O_4$: C, 55.62; H, 7.67. Found: C, 55.42; H, 7.74.

(*Z*)-*N*-*t*-Butyloxycarbonyl-1-[(1'-fluoro-2'-amino)propylidene]-2-cyclopentane Benzoyl Hydroxamate (1a). Hydroxamic acid **15a'** (15.0 mg, 0.050 mmol) was dissolved in dry THF (0.5 mL) and cooled to 0 °C. Pyridine (4.5 μL, 0.056 mmol) was added and the solution was allowed to stirr for 15 min, then a 0.5 mL solution of benzoyl chloride (6.2 μL, 0.053 mmol) in THF was added. A white precipitate formed immediately. The reaction mixture was further stirred for 40 min and was then transferred to a separatory funnel containing 3 mL of ethyl acetate/hexanes (1 : 1). The organic layer was washed with 0.1 *M* HCl (1 mL), H_2O (1 mL), brine (1 mL) and dried over $MgSO_4$. Filtration followed by removal of solvents *in vacuo* yielded the crude product which was purified by chromatography (20 to 30% EtOAc in hexanes) to obtain pure **1a'** (10.2 mg, 51%) as white solid: IR (CCl_4) 3460, 3219 (br,s), 2976, 2870, 1770, 1682, 1506, 1452, 1254, 1166, 1060, 788, 706 cm^{-1}; ^{19}F NMR ($CDCl_3$) δ -123.95 (d, J = 24.5 Hz); ^1H NMR ($CDCl_3$) δ 10.16 (br s, 1H), 8.05 (d, J = 7.0 Hz, 2H), 7.57 (t, J = 7.5 Hz, 1H), 7.42 (t, J = 9.0 Hz, 2H), 4.72 (br s, 1H), 4.29 (dq, J = 26.6, 6.6 Hz, 1H), 3.69 (br s, 1H), 2.73 (m, 1H), 2.32-2.21 (m, 2H), 2.02-1.77(m, 3H), 1.31 (s, 9H), 1.30 (d, J = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 170.34, 164.46, 155.77, 152.89 (d, J = 254.6 Hz), 133.77, 129.97, 128.51, 127.20, 118.11 (d, J = 14.2 Hz), 80.30, 46.25 (d, J = 26.8 Hz), 45.77 (d, J = 2.7 Hz), 32.10, 28.18, 27.72 (d, J = 3.2 Hz), 24.76, 16.95. The other diastereomer **1a"** was made in the same manner in 32% yield: ^{19}F NMR ($CDCl_3$) δ -120.70 (d, J = 23.0 Hz); ^1H NMR ($CDCl_3$) δ 9.53 (br s, 1H), 8.08 (d, J = 8.4 Hz, 2H), 7.60 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.6 Hz, 2H), 4.74 (br s, 1H), 4.49 (dq, J = 26.1, 6.7 Hz, 1H), 3.62 (br

s, 1H), 2.63-2.48 (m, 1H), 2.46-2.32 (m, 1H), 2.26-2.13 (m, 1H), 2.00-1.85 (m, 3H), 1.42 (s, 9H), 1.34 (d, J = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.33, 164.82, 154.89, 154.00 (d, J = 250.7 Hz), 134.12, 129.97, 128.65, 126.73, 117.90 (d, J = 12.6 Hz), 79.85, 45.71 (d, J = 26.6 Hz), 44.16, 30.49, 28.37, 27.76 (d, J = 3.3 Hz), 25.65, 18.10.

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